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Organic chemistry



ORGANIC CHEMISTRY

BY

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AUTHOR'S PREFACE TO THE FOURTH ENGLISH EDITION

In the fourth English edition of this textbook various chapters have been revised and extended and several new sections have been added. For example, sections on the following subjects have now been included: polysiloxanes and other organic silicon compounds, diacyl peroxides and peracids, streptomycin, organic compounds containing isotopic carbon and nitrogen, etc. The following parts have undergone substantial alteration or change: the chapters on elementary microanalysis, mineral oil products, organic lithium compounds, oestrogenic substances (doisynolic acid, synthesis of oestrone), vitamins (pteroylglutamic acid, vitamin A), the colouring matter of blood and related compounds, alkaloids (retronecine alkaloids, solanine-solanidine, N-methylmorphinan synthesis, etc.), and *cyclooctatetraene*.

Throughout the whole subject-matter, the results of the most recent investigations have received mention wherever possible. Likewise, for the designation of the configuration of stereoisomers in certain series, I have introduced in this textbook the symbols D and L (instead of *d* and *l* respectively) which are now coming into more general use in the literature.

I am indebted to those chemists who have made various suggestions since the appearance of the third edition.

Zürich, December 1949

P. KARRER

1079 (1) organic chemistry
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CONTENTS

Part I. Aliphatic Compounds

	page
Chapter 1. Introduction	1
Organic Chemistry	1
Composition and analysis of organic compounds	3
Qualitative detection of elements in organic molecules	3
(a) Detection of carbon and hydrogen.	3
(b) Detection of nitrogen	4
(c) Detection of oxygen	5
Quantitative determination of elements	5
(a) Quantitative determination of carbon and hydrogen	5
(b) Quantitative determination of nitrogen.	6
1. Dumas method	6
2. Kjeldahl method	7
(c) Quantitative determination of halogens, phosphorus, arsenic, sulphur, etc. in organic compounds	8
Quantitative analysis of organic compounds by micro-analytical methods	8
Micro-analytical determination of carbon and hydrogen	9
Micro-volumetric determination of nitrogen as gas (micro-Dumas method)	11
Derivation of chemical formulæ	11
(a) Empirical and Molecular formulæ	11
(b) Structural or Constitutional formulæ	14
Historical review of the development of the formulation of organic compounds	17

Section I. Hydrocarbons and Compounds with a Monovalent Function

Chapter 2. Hydrocarbons	22
Saturated hydrocarbons or Paraffins.	22
The Geneva Nomenclature.	24
Natural occurrence of paraffin hydrocarbons	26
Methods of preparation of paraffin hydrocarbons	26
Physical properties of the paraffins	30
Chemical properties of the saturated hydrocarbons	32
Individual members of the paraffin series of hydrocarbons	33
Methane	33
Ethane	34
Propane	35
Butanes	35
Pentanes, hexanes, heptanes	35
Octanes	36
Higher paraffin hydrocarbons	36
Mineral Oil	37
Unsaturated aliphatic hydrocarbons.	43
Olefins or hydrocarbons of the ethylene series	44

	page
Structure and spatial configuration of the olefins	44
Nomenclature of the olefins	49
Occurrence and preparation of the olefins	50
Physical properties of the olefins	52
Chemical properties of the olefins	53
Methylene	57
Ethylene	57
Higher olefins.	57
Unsaturated hydrocarbons with two or more double bonds, C_nH_{2n-2} , C_nH_{2n-4} , etc.	58
1. Compounds with isolated double bonds	58
2. Hydrocarbons with cumulative double bonds	59
3. Hydrocarbons with conjugated double bonds	59
The electronic concept of the carbon bond and the carbon double bond.	62
Hydrocarbons of the acetylene series.	66
Methods of preparation of the acetylenic hydrocarbons	67
Metallic derivatives of the acetylenic hydrocarbons	67
Acetylene.	68
Chapter 3. The Monovalent Halogen Function: Alkyl Halides, Alkylene Halides.	72
Alkyl halides.	72
Methods of preparation.	72
Properties of the alkyl halides	75
Monohalogen derivatives of unsaturated hydrocarbons.	77
Chapter 4. The Monovalent Hydroxyl Function: Monohydric Alcohols	80
Occurrence and preparation of the alcohols	81
Physical properties of the alcohols	84
General chemical properties of the alcohols	85
Methyl alcohol	87
Ethyl alcohol	88
Alcoholic fermentation	89
Propyl alcohols	95
Butyl alcohols.	96
Amyl alcohols.	96
Optical activity	98
Higher alcohols	108
Unsaturated alcohols.	108
Esters of the alcohols with inorganic acids	111
Esters of the halogen hydracids.	111
Esters of nitrous acid	111
Esters of nitric acid	112
Esters of hypochlorous acid	112
Esters of sulphuric acid	112
Esters of sulphurous acid.	113
Esters of phosphoric acid	114
Esters of boric acid	114
Esters of silicic acid	114
Ethers	115
Preparation	115
Properties	116
Chapter 5. The Monovalent Sulphur Function: Alkyl Sulphur Com- pounds	119
Thioalcohols, Mercaptans.	119
Thioethers. Alkyl sulphides	121
Sulphoxides and sulphones.	123
Alkylsulphonic acids	123

	page
Chapter 6. <u>Monovalent Nitrogen Functions</u>	124
I. Amines	124
Electronic formulation of the "onium compounds" and related substances	125
Methods of preparation	128
Properties of amines.	131
II. Alkyl derivatives of hydrazine	136
III. Alkyl derivatives of hydroxylamine	137
IV. Aliphatic nitro-compounds.	137
Chapter 7. <u>Organic Derivatives of Other Elements</u>	141
Aliphatic phosphorus compounds	141
Aliphatic arsenic compounds	143
Aliphatic antimony and bismuth compounds	145
Aliphatic silicon compounds (Silanes)	145
Aliphatic germanium compounds	148
Organic compounds of tin	148
Organic compounds of lead	150
Organic compounds of boron.	151
Organic compounds of aluminium ✓	151
Organic compounds of magnesium ✓	151
Organic compounds of zinc ✓	154
Organic compounds of cadmium	154
Organic compounds of mercury	155
Organic compounds of copper, silver, gold, and platinum	155
Organic compounds of chromium.	155
Organic compounds of the alkali metals	155

Section II. Compounds with a Divalent Function

Chapter 8. <u>The Divalent Halogen Function: Gem.-Dihalogen Derivatives</u>	157
Chapter 9. <u>The Divalent Oxygen Function: Aldehydes and Ketones</u>	158
✓ Aldehydes.	158
Methods of formation	158
Physical properties	159
Chemical reactions	160
Formaldehyde. Methanal	166
Acetaldehyde. Ethanal	168
Higher aldehydes.	169
Unsaturated aldehydes	169
Ketones.	172
Methods of formation	172
Physical properties	174
Chemical properties.	174
Acetone.	176
Higher ketones.	178
Unsaturated ketones	178
Ketenes.	180

Section III. Compounds with a Trivalent Function

Chapter 10. <u>The Trivalent Halogen Function</u>	182
Chloroform	182
Bromoform	183
Iodoform	183
Fluoroform	184

	page
Chapter 11. Trivalent Nitrogen Functions. Hydrocyanic acid. Nitriles	184
Hydrocyanic acid, or Prussic acid.	184
Nitriles	187
Preparation	187
Physical properties	188
Chemical properties.	188
Isonitriles	189
Chapter 12. The Trivalent Oxygen Function. Monobasic Carboxylic Acids	190
Saturated monobasic carboxylic acids. Fatty acids.	190
Nomenclature	191
Methods of formation	191
Physical properties	193
Chemical properties.	194
Formic acid	198
Acetic acid	200
Propionic acid	201
Butyric acids.	202
Valeric acids.	202
Higher fatty acids	203
Monobasic unsaturated acids with ethylenic linkages; acrylic or oleic acid series	205
Synthesis	205
Properties	205
Unsaturated carboxylic acids with two or three ethylenic linkages	209
Unsaturated carboxylic acids with triple bonds	210
Esters of the carboxylic acids.	210
Methods of formation	210
Properties	212
Fruit essences	212
Waxes	212
Fats and oils.	213
Phosphatides.	218
A. Ester phosphatides.	218
B. Acetal phosphatides	219
Esters of the ortho-carboxylic acids	220
Acid halides of the carboxylic acids	220
Acid anhydrides	221
Diacyl peroxides and Peracids	222
Acid amides	223
Imido-ethers. Amidines	224
Hydroxamic acids	225
Acid hydrazides. Hydrazidines. Acid azides.	226

Section IV. Compounds with Tetravalent Functions

Chapter 13. Simple Tetrasubstitution Products of <u>Methane</u>	227
Tetravalent halogen function.	227
Halogen-, sulphur-, and nitrogen-containing derivatives of carbonic acid	228
Phosgene, carbonyl chloride	228
Chlorocarbonic esters	229
Carbon oxysulphide.	229
Carbon disulphide	229
Carbamic acid and its derivatives.	230
Urea	231
Guanidine.	233
Thiourea	234

	page
Cyanic acid	235
Fulminic acid	238
Thiocyanic acid	239

Section V. Compounds with Two Functions in the Molecule

Chapter 14. Compounds with Two Monovalent Functions	241
Dihalogen compounds.	241
Glycols	243
Mono- and di-thioglycols	247
Amino-alcohols.	247
Diamines	249
Chapter 15. Polyhalogen Compounds. Halogen Derivatives of Aldehydes and Carboxylic Acids	252
I. Polyhalogen derivatives	252
II. Halogen derivatives of the aldehydes and carboxylic acids	253
Chloral	253
Halogen-substituted fatty acids	253
Chapter 16. Oxidation Products of Glycol.	255
Hydroxyaldehydes. Hydroxyketones.	255
Dialdehydes. Diketones	257
Monohydroxycarboxylic acids	261
Aldehydic carboxylic acids.	265
Keto-carboxylic acids	266
Pyruvic acid	266
Acetoacetic acid	267
Lævulinic acid	271
Chapter 17. Cyanogen. Dicarboxylic Acids	272
I. Cyanogen	272
II. Free thiocyanogen	273
III. Saturated dicarboxylic acids	273
Oxalic acid	275
Malonic acid.	277
Succinic acid.	279
Glutaric acid.	280
Adipic acid	280
Pimelic acid	281
Suberic acid	281
Azelaic acid	281
Sebacic acid	281
Higher dicarboxylic acids	281
IV. Unsaturated dicarboxylic acids.	281
Maleic and fumaric acids	281
Citraconic, mesaconic, and itaconic acids	284
Chapter 18. Aminocarboxylic acids and Proteins	285
I. Aminocarboxylic acids	285
Occurrence and methods of preparation	285
Properties	289
Aliphatic diazo-compounds	293
Polypeptides	296
Stereochemistry of the α -amino-acids	300
II. Proteins	304
Composition and structure.	304
Types of proteins	307

Section VI. Compounds with Three or More Functions in the Molecule

	page
Chapter 19. Polyalcohols	308
Glycerol.	308
Erythritol.	311
Pentaerythritol.	313
Pentitols.	313
Hexitols.	314
Heptitols	314
Chapter 20. Oxidation Products of Polyhydric Alcohols (with the ex- ception of the true Carbohydrates)	315
Tartronic acid	315
Malic acid.	315
Oxal-acetic acid	316
Mesoxalic acid.	317
Tartaric acids	317
Citric acid.	319
Chapter 21. Carbohydrates	321
I. Monosaccharides.	321
Occurrence of monosaccharides.	322
Physical properties	322
Chemical properties.	325
Configuration of the sugars and their immediate derivatives.	333
Synthesis of natural sugars	342
Detection of sugars	344
Individual monosaccharides	344
Glucuronic acid. Galacturonic acid. Mannuronic acid	347
Amino-sugars	348
Chitin	349
II. Oligosaccharides	350
Individual oligosaccharides.	352
A. Disaccharides	352
B. Trisaccharides.	355
C. Tetrasaccharides, Pentasaccharides	356
III. Polysaccharides	356
Starch	357
Glycogen	360
Inulin.	360
Galactogen	361
Yeast glucan and laminarin	361
Pectins	361
Cellulose	362
Wood. Lignin	365
Lichenin (reserve cellulose)	366
Hemicelluloses	367
Artificial silk.	367
Staple rayon	368

Part II. Carbocyclic Compounds

A. Aromatic Compounds

Chapter 22. Introduction. Constitution of Benzene	373
Constitution of benzene	374
Substitution isomerism in the benzene series	381

Section I. Compounds with a Monovalent Function

Chapter 23. Aromatic Hydrocarbons	383
Benzene	383
Homologues of benzene	390
Hydrocarbons with more than one uncondensed benzene nucleus	395
Aromatic hydrocarbons with 'trivalent' carbon	400
Unsaturated aromatic hydrocarbons.	402
Aromatic hydrocarbons with condensed benzene nuclei	405
Naphthalene	405
Acenaphthene	409
Perylene.	409
Anthracene	409
Phenanthrene	411
Chapter 24. Halogen Derivatives of Aromatic Hydrocarbons	413
Benzene derivatives substituted with halogen in the side chain	417
Chapter 25. Nitro-compounds of Aromatic Hydrocarbons	418
Nitro-compounds with the nitro-group in the sidechain	421
Chapter 26. Nitroso- and Hydroxylamine Derivatives of Aromatic Hydrocarbons.	422
Nitroso-compounds	422
Hydroxylamine derivatives.	423
Chapter 27. Aromatic Sulphonic Acids and their Reduction Products	424
Sulphinic acids.	425
Thiophenols	426
Halogeno- and nitrobenzene sulphonic acids	426
Chapter 28. Phenols	427
Monohydric phenols	427
Preparation of phenols	427
Properties of phenols	429
Individual monohydric phenols.	431
Polyhydric phenols	434
Dihydroxy, benzenes	434
Trihydroxy, benzenes	439
Polyhydroxy, benzenes	441
Naphthols	442
Hydroxyanthracenes	443
Hydroxy-derivatives of stilbene.	444
Chapter 29. Halogenated Phenols, Sulphonated Phenols, and Nitro-phenols.	445
Halogen derivatives of phenols	445
Phenol- and naphtholsulphonic acids	445
Nitrophenols.	447

	page
Chapter 30. Aromatic Alcohols	450
Chapter 31. Aromatic Amines	451
Methods of preparation	451
Properties of aromatic amines	453
Aromatic monoamines.	454
Aniline	454
Homologues of aniline.	457
Aromatic diamines	458
Aminonaphthalenes.	461
Aromatic amines with the amino-group in the side chain.	462
Halogen derivatives of aromatic amines	463
Nitro-derivatives of aromatic amines	464
Sulphonic acids of aromatic amines	465
A. Sulphonic acids of aniline.	465
B. Sulphonic acids of the naphthylamines	466
Aminophenols	468
Chapter 32. Acid Derivatives of the Aromatic Amines	469
Organic acyl derivatives of the aromatic amines.	469
Inorganic acid derivatives of amines	471
1. Thionylamines.	471
2. Sulphamic acids	471
3. Nitranilides	471
4. Nitrous acid derivatives. Diazonium salts	472
Substitution of the diazo-group by other radicals	476
Reduction and oxidation of diazonium salts	480
Chapter 33. Azo-Compounds. Azo-Dyes.	481
Colour and dyes	484
Individual azo-dyes.	487
a. Basic azo-dyes	487
b. Acidic azo-dyes.	488
c. Mordant dyes and chrome dyes.	491
d. Direct or substantive cotton dyes	492
e. Azo-dyes produced on the fibre. Ice colours.	495
Azoxy-compounds	496
Chapter 34. Aromatic derivatives of hydrazine.	497
Hydrazo-compounds	497
Tetraarylhydrazines	499
Chapter 35. Aromatic Phosphorus, Arsenic, and Antimony Compounds	500
Phosphorus derivatives	500
Arsenic compounds	500
Antimony compounds.	503
Aryl alkali-metal compounds.	503

Section II. Compounds with Di- and Trivalent Functions

Chapter 36. Aromatic aldehydes.	504
Benzaldehyde	504
Other aromatic aldehydes	506
Chapter 37. Aromatic ketones	509
Methods of preparation	509
Properties	511

	page
Individual ketones	514
Unsaturated ketones	516
Hydroxy-ketones	517
Chapter 38. Simple Aromatic Carboxylic Acids.	521
Benzoic acid.	521
Derivatives of benzoic acid.	522
Benzonitrile, phenyl cyanide.	524
Homologues of benzoic acid	524
Unsaturated aromatic carboxylic acids.	525
Vulpinic acid	528
Chapter 39. Polybasic Aromatic Carboxylic Acids	529
Chapter 40. Chloro-, Nitro-, and Amino-derivatives of aromatic carboxylic acids	533
Chlorobenzoic acids.	533
Nitrobenzoic acids	533
Aminobenzoic acids.	534
Chapter 41. Aromatic Hydroxy-acids	535
A. Hydroxy-acids with a phenolic nature	535
1. Monohydroxy carboxylic acids	535
2. Dihydroxy carboxylic acids	539
3. Trihydroxy carboxylic acids	544
4. Tannins	545
B. Aromatic hydroxy-acids with an alcoholic nature	548

Section III. Pyrone compounds. Indigo dyes

Chapter 42. Derivatives of α - and γ -pyrone	550
A. Derivatives of α -pyrone	550
Coumarin derivatives	551
Derivatives of dibenzo- α -pyrone	553
B. Derivatives of γ -pyrone	554
Chromone	554
Flavone.	555
Flavone derivatives	556
Flavanone derivatives.	559
Isoflavone derivatives	560
Dyes of brazil wood and logwood	560
Xanthone	561
Chapter 43. Anthocyanins. Catechins	562
Catechins	566
Chapter 44. Indigo Dyes.	567
Indigo.	567
Indigo derivatives	573
Thio-indigo. Indigoids.	574

Section IV. Quinones

Chapter 45. Benzoquinones and their simpler Derivatives	576
Individual quinones.	579
Derivatives of benzoquinones.	582
A. Quinone oximes.	582

	page
B. Quinonimines	582
C. Indophenols. Indamines	583
Aniline black	585
Chapter 46. Naphthaquinones. Phenanthrenequinone	587
Dyes derived from the naphthaquinones	587
Phenanthrenequinone	590
Chapter 47. Anthraquinone and its derivatives	591
Anthraquinone	591
Anthraquinonesulphonic acids	592
Hydroxyanthraquinones	592
Trihydroxyanthraquinones	597
Polyhydroxyanthraquinones	597
Aminoanthraquinones	599
Vat dyes of the anthraquinone series	601
(a) Indanthrene dyes	601
(b) Flavanthrene dyes	601
(c) Benzanthrone dyes	602
(d) Anthraquinonimine dyes and acylaminoanthraquinones	603
(e) Anthraquinoneacridone dyes	605
Chapter 48. Dyes derived from Fuchsone	605
Hydroxy-derivatives of fuchsone	609
Fuchsonimonium dyes	610
(a) Malachite green class	610
(b) Fuchsin class	611
Chapter 49. Quinone dyes with closed rings.	615
A. Phenazine dyes	615
Phenylphenazonium salts	617
B. Oxazine dyes	621
C. Thiazine dyes	623
D. Sulphur dyes	626
Blue sulphur dyes	627
Yellow sulphur dyes	629
E. Acridine dyes	630
F. Xanthylum salts	633
(a) Pyronines	633
(b) Rosamines	634
(c) Rhodamines	634
(d) Fluoresceins	635

B. Alicyclic Compounds

Chapter 50. Introduction	637
Natural occurrence of naphthenes, terpenes, and camphors	637
Syntheses of alicyclic compounds	638
Ring-fission of alicyclic compounds	640
Conversion of one ring system into another.	642
(a) Methods of ring contraction	642
(b) Methods of ring expansion	643
Chapter 51. Cyclopropane and its derivatives.	645
Chapter 52. Cyclobutane and its derivatives	649

	page
Chapter 53. Cyclopentane and its derivatives.	652
Fulvenes	653
Ketones of the <i>cyclopentane</i> series	654
Carboxylic acids of the <i>cyclopentane</i> series	656
Chapter 54. Cyclohexane and its derivatives (excluding aromatic com- pounds).	659
Connection between <i>cyclohexane</i> derivatives of aromatic and alicyclic character	659
Occurrence and preparation of <i>cyclohexane</i> compounds.	662
Stereoisomerism of the <i>cyclohexane</i> compounds	663
Hydrocarbons of the <i>cyclohexane</i> series.	665
A. Saturated hydrocarbons	665
B. Unsaturated hydrocarbons with one double bond	666
C. Unsaturated hydrocarbons with two double bonds	668
<i>Cyclohexatriene</i>	673
Alcohols of the <i>cyclohexane</i> series	674
Hydroxyl derivatives of <i>cyclohexane</i>	674
Alcohols derived from <i>p</i> -menthane	678
Aldehydes and ketones of the <i>cyclohexane</i> series	682
Aldehydes.	682
Saturated ketones.	682
Unsaturated ketones	684
Exocyclic ketones of the <i>cyclohexane</i> series	687
Carboxylic acids of the <i>cyclohexane</i> series.	689
Chapter 55. Bicyclic terpenes and camphors (with a six-membered ring) . .	693
Thujane group.	693
Carane group	695
Pinane group	696
Camphane group.	699
Fenchones.	703
Chapter 56. Sesquiterpenes. Polyterpenes. Sterols. Vitamins. Rubber. .	704
Sesquiterpenes. Polyterpenes	704
Carotenoid pigments	708
Sterols	713
Bile acids	716
Sex hormones	717
Hormones of the adrenal cortex	724
Other hormones	724
Digitalis glucosides	724
Saponins	727
~Vitamins	727
Rubber	739
Chapter 57. Cycloheptane and its derivatives.	742
Chapter 58. Cyclooctane and its derivatives. Alicyclic compounds with higher ring systems.	746
Carbon rings with more than eight carbon atoms	748

Part III. Heterocyclic Compounds

Section I. Simpler Heterocyclic Compounds with more or less Aromatic

Nature	755
Chapter 59. Five-membered Heterocyclic Rings with one Hetero-atom	757
Furan group.	757
Furan.	758
Coumarone	761
Thiophen group	764
Thiophen	764
Homologues of thiophen.	766
Thionaphthen	766
Pyrrole group	768
Pyrrole	769
Homologues of pyrrole	771
Colouring matter of blood	772
Bilirubin	776
Chlorophyll	778
Reduction products of pyrrole	781
Carboxylic acids of pyrrole and its hydrogenation products	781
Indole group.	783
Carbazole	788
Phthalocyanines	788
Chapter 60. Five-membered Heterocyclic Rings with two or more Hetero-atoms.	789
A. Five-membered rings with two hetero-atoms.	790
Oxazole derivatives.	790
Thiazole derivatives.	791
Penicillin	792
Imidazole (glyoxaline) and its derivatives	793
Pyrazole and its derivatives	796
B. Five-membered heterocyclic rings with three or more hetero-atoms	800
Furazans	800
1 : 2 : 3-Triazoles.	800
1 : 2 : 4-Triazoles.	802
Tetrazole	803
Chapter 61. Six-membered Heterocyclic Rings with One Hetero-atom	804
Pyran derivatives.	804
Pyridine and its derivatives	806
Quinoline compounds.	811
Isoquinoline	816
Chapter 62. Six-membered Heterocyclic Rings with two or more Hetero-atoms.	817
Diazines.	817
Pyrimidines	818
Pyrazines	820
Purine compounds	823
Uric acid	823
Xanthine	827
Hypoxanthine	828
Adenine.	828
Guanine.	829

Nucleic acids.	page
Pterins	829
Triazines	833
Tetrazines	834
	836

Section II. Alkaloids

Chapter 63. Definition. Occurrence. Isolation	837
Chapter 64. Alkaloids of the phenyl-ethylamine type	839
Ephedrine and Pseudoephedrine	839
Tyramine	840
Hordenine.	841
Mezcaline.	841
Chapter 65. Alkaloids with a Pyrrole Nucleus.	842
Stachydrine	842
Betonicine and Turicine.	842
Hygrine.	843
Cuscohygrine	843
Nicotine.	843
Chapter 66. Pyridine Alkaloids	846
1. Hemlock alkaloids	846
Coniine	846
γ -Coniceine	847
Conhydrine	848
2. Trigonelline.	849
3. Areca alkaloids	849
Arecaidine and arecoline	850
Guvacine and guvacoline	850
4. Alkaloids of pepper.	851
Piperine.	851
5. Ricinine, Lobeline, Anabesine	851
Chapter 67. Alkaloids with condensed Pyrrolidine and Piperidine rings	853
1. Atropine group	853
Atropine	853
Tropeines	857
Hyoscyamine	858
Convolamine.	858
Scopolamine	858
2. Cocaine group.	859
Cocaine.	859
Tropacocaine	862
Cinnamylcocaine	862
α - and β -Truxilline	862
Benzoylecgonine	862
3. Alkaloids of Pomegranate bark.	862
Pseudopelletierine	863
Isopelletierine	864
4. Alkaloids of the Broom and Lupin group	864
Lupinine	864
Sparteine	865

	page
Chapter 68. Cinchona Alkaloids (Alkaloids with a Quinoline ring) . . .	865
Cinchonine	866
Cinchonidine	868
Quinine.	869
Quinidine	874
Cupreine	874
Chapter 69. Alkaloids with an Isoquinoline ring	874
1. Anhalonium alkaloids. Salsoline	874
2. Papaverine group	876
Papaverine	876
Laudanosine.	877
Laudanine.	878
Laudanidine.	878
Narcotine	878
Narceine	882
Hydrastine	883
3. Berberine group	884
Berberine	884
Canadine	887
Corydaline	887
Chapter 70. Morphine and Cryptopine Alkaloids. Colchicine.	888
1. Morphine alkaloids.	888
Morphine and Codeine	888
Thebaine	893
2. Colchicine	895
3. Alkaloids of the Cryptopine type.	896
Chapter 71. Carboline Alkaloids. Vasicine (Peganine)	897
Harmine alkaloids	897
Yohimbine	898
Evodiamine. Rutæcarpine	899
Vasicine (Peganine).	899
Chapter 72. Alkaloids of Ergot, Pilocarpine, Eserine, Cytisine, Solanine, Strychnine, and Alkaloids of Unknown Constitution.	900
Alkaloids of ergot	900
Pilocarpine	901
Solanine. Solanidine	902
Aconitine	903
Cytisine	903
Emetine.	903
Physostigmine or eserine.	903
Strychnine and brucine	904
The biological formation of the alkaloids	905
Robinson's theory of the phytochemical synthesis of alkaloids	906

Part IV. Organic Compounds with Heavy Hydrogen and Heavy Oxygen

Chapter 73. Organic Compounds containing Isotopic Elements	911
1. Compounds with heavy hydrogen	911
Methods of preparation	912
Properties	914

	page
2. Compounds with carbon isotopes	916
3. Compounds with heavy oxygen	917
4. Compounds with nitrogen isotopes	918

Tables

Principal compounds occurring in coal-tar	922
Compounds definitely detected in coal-tar, arranged in order of boiling points	923
Number of structural isomerides of some aliphatic compounds	928
Number of isomerides of paraffins and alcohols	928
Number of structural isomerides of cyclic hydrocarbons	929
Number of structural isomerides of the substitution products of some cyclic parent compounds	929
World production of coal, 1938.	930
Estimate of the coal reserves of the world (1936)	930
Increase in the production of mineral oil	931
Estimate of world sugar production	931
Comparison of the world production of beet sugar and cane sugar (1893-1939)	932
Relative sweetness of various organic substances	932
Classification of odours	933
Minimal concentrations of some perfumes which can be detected	933
Most important poisonous compounds occurring in industry	934
Best-known poisonous substances used in warfare	935
Effects of corrosive and poisonous gases and vapours	936
Limits of tolerance of human beings towards poisonous substances	937
World production and use of the more important textiles	937
Amount of cotton, natural silk, and artificial silk produced by the most important producing countries	937
The best-known artificial materials	938
Comparison of properties of some explosives	939
Dissociation constants of some important organic bases	939
Dissociation constants of the more important organic acids	940
Intervals over which indicators change colour	940
Constants of normal primary alcohols	941
Atomic refractions	941
Important dates in the history of Organic Chemistry	943
Index	949

PART I
ALIPHATIC COMPOUNDS

CHAPTER 1. INTRODUCTION

Organic Chemistry

Several substances which to-day are classed as organic, were known in ancient times, though their preparation in a state of purity was not carried out until much later. Even prehistoric peoples and those at the primitive stage of civilization knew how to convert sweet fruit juices into alcoholic beverages by fermentation; wine was made from grapes, the ancient Egyptians made a kind of beer from barley, and mead was prepared from honey. The rectification of alcoholic liquids, i.e. increasing the proportion of alcohol by distillation, was discovered much later, in the time of the Alchemists (about 900 A.D.), and the name *alcohol*, which the ancient Arabs used to denote any easily volatile substance (*al-Kohol*), was first given to this substance by Paracelsus, and is reserved for it to-day.

It is clear that the souring of wine, which, as we now know, is brought about by the agency of acetic fungi, did not escape the notice of ancient peoples. Acetic acid is, therefore, the longest known of all organic acids, and it remained the only one for thousands of years. Not until the XVIth century were benzoic and succinic acids discovered, and between 1769 and 1785 a number of other organic acids, viz. tartaric, oxalic, citric, malic, mucic, and lactic acids, were isolated as a result of the successful work of Scheele¹.

The first knowledge of some natural colouring matters also goes back to primitive times; the colouring matter of the purple snail (purple of the ancients; Tyrian purple), indigo, and the dye obtained from the madder root (alizarin) were used. Their application presupposes a fairly well developed technique of dyeing even at those times, since the deposition of the colour on to textiles is only possible under definite conditions.

Individual constituents of the animal organism were not isolated until much later. In 1773 Rouelle discovered urea in urine.

In the middle of the XVIIIth century, when the discoveries of new compounds derived from the vegetable and animal kingdom were accumulating, and it was perceived that these substances, in their general behaviour and composition, differed essentially from the "mineral" compounds then known, a first attempt was made to distinguish between substances isolated from organisms and "inorganic" substances, for purposes of classification. The first distinction of this kind appears to have been made by T. Bergmann (1777), and a little later by F. A. C. Gren (1796). Berzelius used the term "*organic chemistry*" shortly afterwards (1806),

¹ For the history of chemistry see: GRAEBE, *Geschichte der organischen Chemie*, Berlin, (1920). — H. G. DEMING, *In the Realm of Carbon*, New York, (1930). — R. J. FORBES, *Bitumen and Petroleum in Antiquity*, Leiden, (1936). — A. FINDLAY, *A Hundred Years of Chemistry*, London, (1937). — PAUL WALDEN, *Geschichte der organischen Chemie seit 1880*, Berlin, (1941).

but, according to E. O. von Lippmann, it is to be found already in the writings of the romanticist Novalis (1772–1801).

It was soon clear to Lavoisier that the elements carbon, hydrogen, oxygen, and nitrogen, play the chief part in the structure of substances which go to compose plants and animals. It impressed Berzelius still more keenly that in this limitation of the number of elements in organic compounds there was a direct contrast to inorganic matter. Of course, he was also aware that *very small amounts* of other elements (calcium, potassium, iron, etc.) occurred in the cells of organisms.

Until the first decades of the XIXth century the view prevailed that compounds which are produced by plants and animals owe their formation to the action of a special force, the *vital force*, and that the “crude and vulgar inorganic forces”, which determine the behaviour of inorganic substances, play no part in living nature. According to this view, organic substances differ from inorganic ones in that their formation depends on this special vital force; it was supposed to be impossible to prepare them artificially by the usual methods of inorganic chemistry.

Ideas of the kind of this hypothetical vital force were obviously only very general and vague. Berzelius said in his *Lehrbuch* (1827) that “the vital force lies completely outside inorganic elements, and does not represent any of their original properties, such as density, impenetrability, electrical polarity, etc. but what it is, how it is produced, and how it ends, we cannot comprehend.”

The principle of classifying chemical compounds into inorganic and organic, based on the existence of a vital force, could be disposed of at once if it were possible to make synthetically in the laboratory, by means of “inorganic” forces, a substance which is produced by living cells. This was done by Wöhler, who, in 1824, prepared oxalic acid from cyanogen, and in 1828, urea from ammonium cyanate; the latter synthesis was of special importance for the further development of organic chemistry.

The hypothesis of a vital force had, however, penetrated so deeply the thought of that time that even Wöhler’s discovery could cause no general refutation of it. Even in 1847, Berzelius held firmly to the idea of a vital force, and in 1842, Gerhardt doubted the possibility of obtaining synthetically the important vital products of organisms such as sugar, uric acid, and so on. However, the rapidly succeeding artificial preparation of many organic compounds refuted such views and caused the gradual disappearance of the hypothesis of the vital force.

For a short time — to some extent indeed even before Wöhler — an attempt was made to base the classification of Chemistry into Inorganic and Organic on the supposition that inorganic compounds were compounds of *simple radicals*, and that organic compounds were derivatives of *complex radicals* [Dumas, Liebig (1837)]. This was due to the mistaken idea that the molecules of the inorganic substances then known were more simple in structure than organic ones. This view was soon shown to be untenable, since, on the one hand the concept of the radical was uncertain, and the composition of radicals was variable, and on the other hand, cases came to light of the existence of complex radicals amongst inorganic compounds.

It was gradually realized that carbon is an element present in all “organic” substances, and that this is characteristic of them. In 1848, Gmelin, in his *Handbuch*, referred to carbon as the one essential constituent of organic compounds. The modern division of chemistry into inorganic and organic is based on this fact.

Organic chemistry is the chemistry of carbon compounds; inorganic chemistry comprises the study of the compounds of all other elements. There are, of course, certain borderline cases, where the boundary between the two classes is not clearly defined. Thus, carbon monoxide, CO , carbon dioxide, CO_2 , carbonic acid, H_2CO_3 , and the carbonates are so intimately connected with the inorganic branch that they are ordinarily dealt with in inorganic chemistry. The hydrocarbons, on the other hand, are classed with organic compounds, and form the parent substances of the system of organic compounds.

The question remains to be discussed whether, and perhaps, why, it is advisable to separate the compounds of a single element, carbon, from all others. Chemical technique does not demand it, since the methods applied in the synthesis of both inorganic and organic compounds are analogous, or at any rate do not contrast. Also, the fact that the empirical formula does not, as a rule, suffice for one particular carbon compound, but that often many organic compounds of the same composition, but differing in molecular structure, or in arrangement of the atoms in space, can exist, can no longer be regarded as a characteristic of organic matter, since similar behaviour has been observed in many inorganic substances. *It is the immense number of carbon compounds at present known, which far exceeds the number of inorganic substances, that justifies, and indeed demands, a special treatment for this class of substances.* The advantage of this distinction is thus primarily didactic. Normally there is found a closer physical-chemical-physiological connection between compounds of carbon than between most inorganic substances, since the latter are derived from the most diverse elements.

The comprehensiveness and variety of carbon chemistry is a striking and unique phenomenon. In a later chapter these exceptional characteristics of carbon will be more fully explained.

Composition and analysis of organic compounds¹

As has been stated above, Lavoisier and Berzelius were the first to point out that carbon, hydrogen, oxygen, and nitrogen played the most important part in the structure of organic matter. These fundamental elements have therefore sometimes been called *organogenic* elements. In addition, however, certain other elements are to be found in naturally occurring organic compounds. Sulphur is found in many proteins; constituents of the cell nucleus, lecithins and phosphatides, contain phosphorus; the red colouring matter of blood contains iron, chlorophyll contains magnesium, and, in the blue blood of arthropods and some molluscs, copper complexes are found.

It is now possible to make "organic" compounds with the majority of elements, i.e. to combine the latter with carbon, by synthetic methods. Later chapters will provide numerous examples of such substances.

QUALITATIVE DETECTION OF ELEMENTS IN ORGANIC MOLECULES

(a) **Detection of carbon and hydrogen.** There are certain carbon compounds which burn with very sooty flames, e.g. benzene, and acetylene. The

¹ J. F. THORPE and M. A. WHITELEY, *A Student's Manual of Organic Chemical Analysis, Qualitative and Quantitative*, London, (1925). — R. L. SHRINER and R. C. FUSON, *The Systematic Identification of Organic Compounds*, New York, (1935).

fact that they contain carbon can therefore be inferred from the formation of soot, i.e. separation of carbon. This test for carbon, however, is not trustworthy since very many organic substances burn with non-luminous flames, and without deposition of soot, and others, such as chloroform and carbon tetrachloride, will not burn at all.

Carbon and hydrogen can always be detected by heating the dry substance with granular copper oxide, or lead chromate. The carbon is converted into carbon dioxide and the hydrogen is oxidized to water. The latter is recognized by the condensation of drops of water; the carbon dioxide is detected in the usual way with baryta water (fig.1).

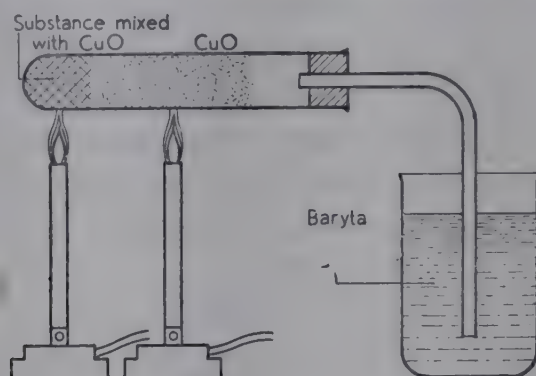


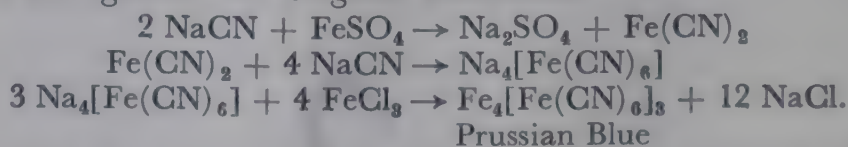
Fig. 1

(b) **Detection of nitrogen.** Many, but not all, organic compounds containing nitrogen split off their nitrogen in the form of ammonia when heated with dry alkalis, the most suitable of these being soda-lime. The ammonia can be detected by the usual methods (smell, Nessler's reagent, action on mercurous nitrate). The applicability of this test is considerable, but is limited to certain classes of nitrogen compounds. Only a positive response to the test is a definite indication; a negative result does not necessarily mean that the substance tested contains no nitrogen.

Lassaigne's test for nitrogen is of more general application. About 0.1 g of the organic substance is melted with a piece of sodium (or potassium) the size of a pea, in a small glass tube, and strongly heated. The carbon and nitrogen of the compound thus combine with the sodium to give sodium cyanide:



The melt is now dissolved in water, a solution of a ferrous salt is added, and the mixture warmed. The sodium cyanide combines with the ferrous salt to give ferrous cyanide, and the latter combines with four more molecules of sodium cyanide to produce sodium ferrocyanide. When the solution of this salt is acidified and a little ferric chloride solution is added, a blue precipitate (or with very dilute solutions, a blue coloration) of *Prussian Blue* results. A positive result indicates the presence of nitrogen in the original substance.



The Lassaigne test sometimes fails, namely, when the nitrogen in the organic compound is so loosely combined that it is evolved on warming even before the substance melts, and so has no opportunity to combine with the sodium or potassium. In this case, the method of Dumas, which will be described under quantitative methods (p. 6), is used.

(c) **Detection of oxygen.** The amount of oxygen in a compound is usually determined by difference; i.e. all other elements in the substance concerned are determined quantitatively, and the sum of the percentages is subtracted from 100. This difference gives the amount of oxygen present.

H. ter Meulen has recently described a process by means of which oxygen can be directly determined quantitatively. The organic substance containing oxygen is heated in a current of hydrogen, and the resulting mixture of gases is passed over a contact catalyst (nickel), which causes the combination of hydrogen and oxygen, producing water. The latter passes into an absorption apparatus, and is weighed.

QUANTITATIVE DETERMINATION OF ELEMENTS

(a) **Quantitative determination of carbon and hydrogen.** The quantitative determination of carbon and hydrogen is always carried out simultaneously, and depends on the fact that both carbon and hydrogen are oxidized, the former to carbon dioxide and the latter to water. The development of the method is mainly due to Liebig and Glaser. The analysis is carried out using the following apparatus:

Near the end of a tube, made of difficultly fusible glass, or quartz, is a porcelain boat (s) containing the substance to be analysed. In front of, and behind the boat are spirals of oxidized copper gauze (copper oxide spirals). Then follows a layer of granular copper oxide. The tube is placed in a combustion furnace, being supported on an iron trough, and projecting a few centimetres at either end of the furnace (Fig. 2 and 3).

The left-hand end of the tube is connected to a purifying and drying apparatus, which serves to remove carbon dioxide and water from the air or oxygen which is passed through the combustion tube to ensure complete oxidation. The apparatus is usually filled with soda-lime (to absorb carbon dioxide) and calcium chloride (to absorb moisture).

At the other end of the combustion tube are fitted the absorption vessels for carbon dioxide and water, the products of combustion of the substance to be analysed. The absorption apparatus consists first of a U-tube filled with calcium chloride, in which the water is absorbed, and a second tube filled with

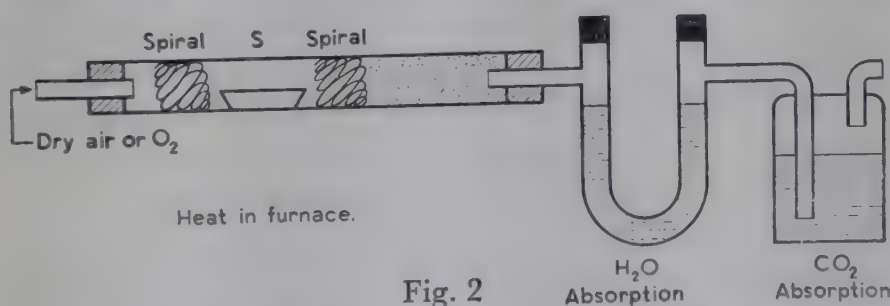


Fig. 2

soda-lime, to absorb carbon dioxide. In place of the soda-lime tube, a bubbler, containing strong caustic potash may be used for the absorption of the carbon dioxide. Finally, there is a second calcium chloride tube, which prevents atmospheric moisture from passing back into the soda-lime tube.

The filled combustion tube, without the substance for analysis, is first heated to redness whilst a stream of pure, dry oxygen is passed through it to remove possible traces of organic compounds. After cooling, the boat containing the weighed substance (0.2–0.3 g) is introduced, and the tube is connected with the

absorption vessels for water and carbon dioxide, which have been accurately weighed. Oxygen is then passed slowly through the apparatus and the heating of the combustion tube is begun, starting with the right-hand end containing the granular copper oxide. When this part is red-hot, the burners nearer the part of the tube containing the substance to be analysed are lighted one by one; finally, the part occupied by the boat is heated to redness.

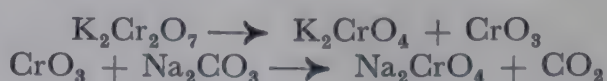
The carbon dioxide and water produced by the combustion travel with the stream of oxygen through the absorption vessels, where they are absorbed. When, after 2–3 hours, the combustion is finished, the absorption vessels are disconnected, stoppered, and, when cool, weighed. The increase over the initial weights of the absorption vessels are the weights of carbon dioxide and water which have been formed from the weighed amount of substance analysed. From these the weight of carbon and hydrogen in the compound can be calculated.

Difficultly combustible substances are first mixed with previously heated, powdered copper oxide, or lead chromate, in the boat; these oxidizing agents aid the combustion considerably.

If the substance to be analysed contains certain other elements, complications may ensue. In this case, a slight change in the filling of the combustion tube is necessary.

If the substance contains *nitrogen*, this is often given off during the combustion in the form of higher oxides of nitrogen, which are retained by calcium chloride and soda-lime, thus indicating too high values for carbon dioxide and water. To avoid this a spiral of reduced copper gauze is placed after the layer of granular copper oxide, and is kept red-hot during the whole of the analysis. This reduces the higher oxides of nitrogen to nitrogen and nitrous oxide which are not absorbed.

Organic substances containing *alkali metals*, for example, the alkali salts of organic acids, also require special treatment when being analysed. The alkali metals are converted during the combustion into the corresponding metal oxides, which combine with the carbon dioxide produced in the oxidation of the carbon, forming alkali carbonates. The latter are stable even at high temperatures, and do not give up their carbon dioxide. The carbon dioxide measured in the analysis will therefore be too low. To prevent this, the substance to be analysed is mixed with some dry, powdered potassium dichromate. The latter decomposes into potassium chromate and chromic acid, which, in turn, reacts with the sodium carbonate to form sodium chromate and CO_2 :



When substances containing *halogens* are to be analysed it is again not sufficient simply to fill the tube with copper oxide. The copper halides which would be formed in the course of the analysis lose part of their halogen on heating to redness, and are also somewhat volatile. This halogen and copper halide would be collected in the absorption apparatus, making the result of the analysis useless. To prevent this a spiral of silver gauze is included in the combustion tube in addition to its normal filling; it retains the volatile halide vapours and halogens as silver halides, which are not decomposed on heating.

(b) **Quantitative determination of nitrogen.** 1. DUMAS METHOD. Of the

quantitative methods of determining nitrogen the one most frequently used in the laboratory is that due to Dumas. The principle of the method is to convert the combined nitrogen of the substance into elementary nitrogen and measure this volumetrically.

The process is carried out in a combustion tube which is filled in exactly the same way as for the carbon and hydrogen determination. The reduced copper spiral placed at the end of the tube is indispensable in this determination.

The fore part of the combustion tube, where the porcelain boat is situated, is connected to a source of carbon dioxide. Usually it consists of a tube containing sodium bicarbonate or magnesium carbonate, from which carbon dioxide is driven off on heating. The further end of the tube is connected by an airtight joint to an azotometer, or eudiometer, in which the gases produced during the combustion are collected over 40 per cent caustic potash in a graduated tube.

Before the combustion tube is heated it is completely filled with carbon dioxide. When the gas passing from the tube into the azotometer is *completely* absorbed, and it is therefore certain that the apparatus contains no air, the heating is commenced. From this point the combustion is carried out exactly as in the determination of carbon and hydrogen described above.

The caustic potash absorbs the water and carbon dioxide produced in the combustion. The nitrogen, on the other hand (any nitrogen oxides produced are reduced to nitrogen by the copper spiral in the tube) passes into the azotometer and at the end of the analysis can be directly determined quantitatively by reading its volume.

The Dumas method can be used for the analysis of all compounds containing nitrogen; the results are good, the nitrogen determined being as a rule 0.1–0.2 per cent too high.

2. KJELDAHL METHOD. Some nitrogenous organic compounds, such as proteins and many others, give off their nitrogen in the form of ammonia when heated with fuming sulphuric acid to which some mercury, or an oxidizing agent (manganese dioxide, potassium permanganate, copper sulphate, potassium dichromate) is added. The oxidation is carried out in long-necked flasks, which are placed on the slant, and the liquid is heated almost to its boiling point. In order to raise the boiling point, potassium sulphate is often added.

After the organic compound has been destroyed, the reaction liquid is diluted with water, made alkaline with sodium hydroxide, and the ammonia liberated is distilled off into standard acid, and is thus determined quantitatively.

This very useful method, of which the accuracy is as great as that of the Dumas method, cannot, unfortunately, be applied to the analysis of all nitrogenous organic compounds. There are substances which do not split off their nitrogen as ammonia when treated in this way, e.g. nitro-, nitroso-, azo-compounds, etc. In the cases mentioned, the difficulty can be overcome by first reducing the substance to an amine, and treating the latter with fuming sulphuric acid. There are a few other nitrogen compounds for which the Kjeldahl process cannot be used. Its chief application is to cases of serial analysis of organic compounds of similar composition. Thus, it is useful in food laboratories, agricultural research stations, etc., for the estimation of the nitrogen content of food and grain. The greatest advantage which the process possesses over the Dumas method lies in the fact that it is possible by means of it to carry out many analyses simultaneously.

(c) **Quantitative determination of halogens, phosphorus, arsenic, sulphur, etc., in organic compounds.** For the estimation of these and similar elements in organic compounds it is usually necessary to destroy the organic part of the molecule completely. This is done in the *Carius* method by means of concentrated nitric acid. In a thick-walled, hard-glass tube, sealed at one end (a so-called "bomb-tube"), about 35–45 cm long, are placed 1.5–2 cm³ of fuming nitric acid. In the estimation of halogens, a small crystal of silver nitrate is also added. A small glass tube (ignition tube) containing the weighed substance, is slipped into the tube, in such a way that the nitric acid does not enter the small tube and come into contact with the substance. The tube is now sealed off and heated in a "tube" or "bomb" furnace to 180°–300° for several hours. After cooling, the point of the tube is withdrawn a little from the furnace and softened by warming in a Bunsen flame. The compressed gases in the tube force an opening through the softened glass, and blow out. The tube is now opened by carefully breaking off the point, and the contents are poured into a beaker, and analysed by the ordinary methods of inorganic analysis.

The carbon and hydrogen of the compound are completely oxidized by treatment with the nitric acid. If the substance contains sulphur, arsenic, and phosphorus, these are now present as sulphuric, arsenic, and phosphoric acids, and can be estimated as such. In the *Carius* method for halogens, the silver nitrate is put into the tube, as mentioned above, so that the halogen set free in the heating is converted into silver halide and precipitated. To estimate it quantitatively it is simply transferred to a Gooch crucible, washed, dried, and weighed.

The breakdown of organic compounds by the *Carius* method finds very extensive application. Many other methods are recommended for special cases, but these are of only secondary importance.

QUANTITATIVE ANALYSIS OF ORGANIC COMPOUNDS BY MICRO-ANALYTICAL METHODS¹

Investigations in physiological chemistry, and of naturally occurring substances, which are in the forefront of recent chemical research, have called forth improved methods of analysis. Frequently the amounts of substances available are so small that it would be very difficult, if not impossible, to determine their composition by the older methods of quantitative organic analysis, which require an amount of substance of the order of 0.1 g for a single determination.

F. Pregl, faced with these difficulties, devised a method of organic micro-analysis in 1912, by means of which it was possible to carry out a carbon-hydrogen or a nitrogen determination with 7–13 mg. of a substance. Later he improved the method to such an extent that 2–4 mg of substance were sufficient for an analysis. By 1916, Pregl's method of analysis was so fully developed that it has not been essentially altered since. It is economical of material and time, and it is simple and accurate. Once the process has been successfully used, no chemist would return to the older method. It is also becoming increasingly used in industry.

¹ See: EMICH, *Lehrbuch der Mikrochemie*, 2nd ed. Munich, (1926). — A. FRIEDRICH, *Die Praxis der quantitativen organischen Mikroanalyse*, Leipzig and Vienna, (1933). — F. PREGL, *Quantitative Organic Microanalysis*, revised by J. GRANT, 4th Engl. ed. — J. B. NIEDERL and V. NIEDERL, *Micromethods of Quantitative Organic Analysis*, 2nd ed., New York, (1942).

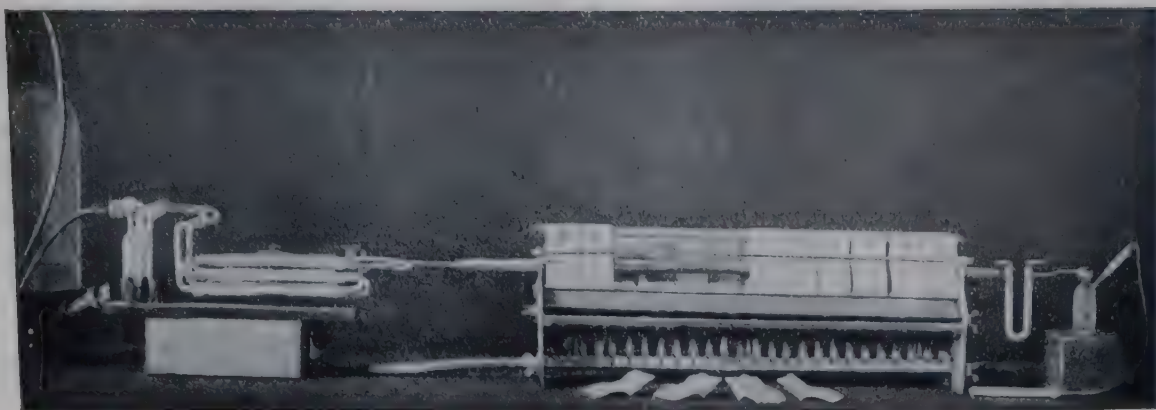


Fig. 3.

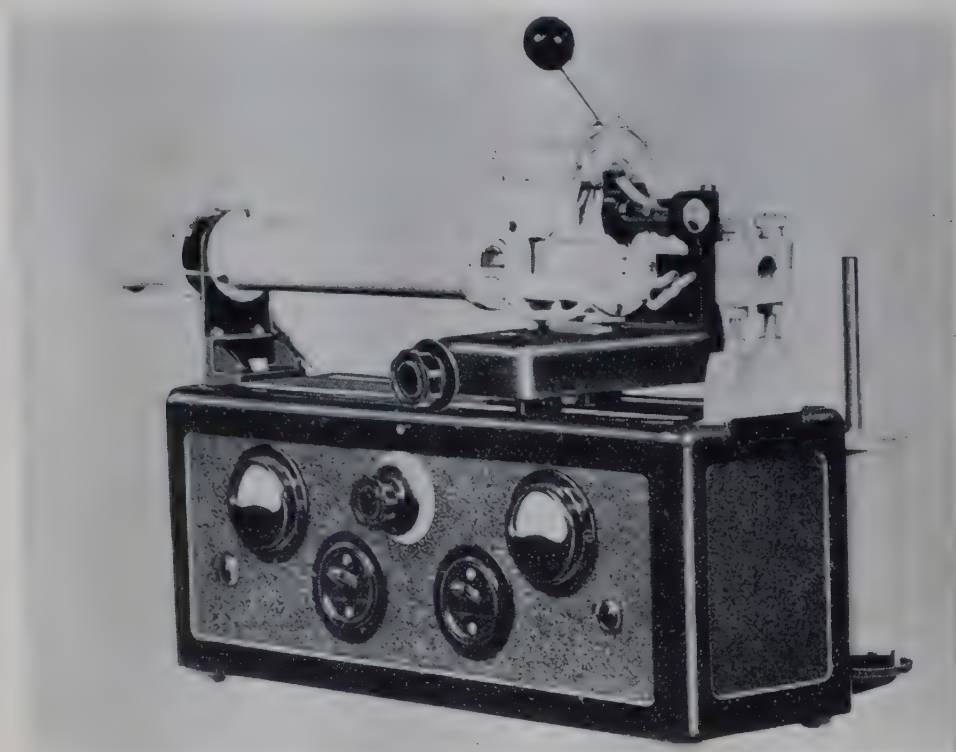


Fig. 4.



Fig. 5.

The first micro-analyses for sulphur and the halogens were carried out by F. Emich (1909). The methods have been improved in more recent times.

A fundamental condition for the success of any micro-analytical method is the existence of a sufficiently sensitive balance. At the instigation of Pregl, a special "micro-chemical" balance for use in quantitative micro-analysis was constructed in the Kuhlmann workshops at Hamburg. This balance has the same sensitivity with a maximum load of 20 g as it has when unladen. As the beam is only 70 mm long it swings very quickly, with the great advantage that the time required for weighing is shortened. The weighings can be easily carried out to an accuracy of ± 0.002 mg. The rider-scale is provided with 100 notches. The balance is only in equilibrium when unladen, if the 5 mg rider is in the first notch at the left-hand end; displacement of the rider by one notch corresponds to 0.1 mg and gives a deflection on the scale of 10 divisions, (which is magnified by mirrors) when the balance swings. A difference in swing of 1 division therefore corresponds to 0.01 mg, and since the swing can be read to at least one-fifth of a division, the accuracy of a weighing is brought to 0.002 mg.

Based on similar principles, a "damped" balance is manufactured by Bunge (Hamburg). Micro-balances are also constructed by the Sartoriuswerke and L. Oertling Ltd. (London).

The micro-analytical determination of carbon and hydrogen. The combustion tube, made of "Supremax" glass has an external diameter of 9.5–10.5 mm., and is about 50 cm long. At one end the tube narrows down to a neck 2 cm long, with an external diameter of 3–3.5 mm, corresponding to the dimensions of the absorption apparatus. The connection between the tube and the absorption apparatus is usually made glass to glass through a piece of thick-walled, paraffin-soaked, rubber tube.

The combustion of simple compounds containing only carbon, hydrogen, and oxygen requires a filling of copper oxide only in the combustion tube. It is, however, desirable to use the so-called universal filling, which allows substances containing any of the other elements, e.g. nitrogen, halogens, sulphur, and also nitro-groups, to be analysed accurately. The filling of such a tube is shown in Fig. 6.

At the narrow end of the tube, first, a length of 1 cm is filled with previously heated thin silver wool. Then follows the so-called retarding plug of asbestos, which is made sufficiently tight, so that, with a water pressure of 6–8 cm, maintained constant by the pressure regulator, a streaming rate of the gas of 3–5 cm³ per minute is obtained. At this speed the carbon of any substance is completely converted to carbon dioxide. The retarding plug is followed by a layer of granular lead dioxide 2–2.5 cm long, which is an excellent absorbent for higher oxides of nitrogen. Next, after a thin layer of asbestos comes a 5 cm long layer of silver and then a filling, 14 cm long, of the oxidation mixture, consisting of equal parts of copper oxide and lead chromate. It is shaken down, and a little asbestos pushed in to keep it in position. Finally, there is a filling of about 1.5–2 cm of silver wool to absorb halogens and sulphur. The use of this lengthens the life of the silver and lead dioxide further down the tube. The oxidation mixture is brought to a red heat using a Teklu burner with a "long burner" attachment. Part of the silver layers at either side extend into the area being heated.

On account of the fact that lead dioxide retains water, the part of the tube containing it must be heated to an approximately constant temperature of 170–190°. This is easily done by means of the decalin boiler. This consists of a hollow tube surrounded by a drum containing decalin; the vertical tube,

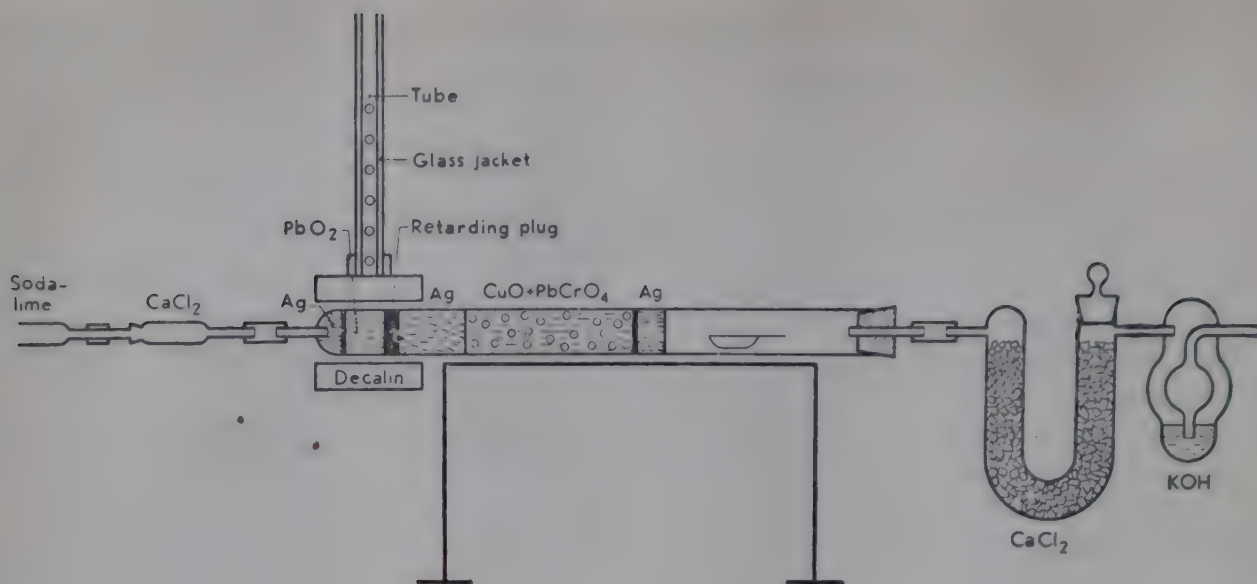


Fig. 6

provided with holes at different heights, which is screwed into the boiler, is surrounded by a glass jacket, held in position by a cork (Verdino's boiler). The boiling of the decalin can thus be observed all the time in the vertical tube. In this way, the lead dioxide is maintained at the temperature of boiling decalin.

For the absorption of water and carbon dioxide, two straight tubes, 8–10 cm long and 8 mm external diameter, divided into compartments, and provided with ground-glass slip-over caps, and capillary exit tubes, are used. The first, the smaller of the two, is filled with calcium chloride or anhydron (anhydrous magnesium perchlorate), the second, and longer, is filled with dry soda-lime and soda-asbestos. The caps are cemented on to the filled tubes with Krönig's glass cement (1 part white wax and 4 parts colophony resin).

It is easy to bring the absorption tubes to constant weight. They weigh 6–9 gms. each.

The resistance which they offer to the flow of gas is overcome by sucking the gas through with a Mariotte's flask, so that the streaming rate through the combustion tube becomes the same as before the absorption apparatus was attached. The drying and the velocity control of the currents of oxygen and air is carried out with a small apparatus, consisting of a U-tube filled with calcium chloride or anhydron, and a bubbler filled with 50 per cent caustic potash.

For analysis 3.5 to 5 mg of the substance are accurately weighed into the platinum boat. In a series of analyses, each one requires 50 to 60 minutes. One filling of the tube may serve for 200 to 300 combustions.

THE ELECTRICAL COMBUSTION FURNACE. The electrical heating of the combustion furnace is to be preferred to gas heating, since almost no radiant heat and particularly no combustion gases reach the surrounding air. In such combustion furnaces all the heating is done electrically. The length of the long heater in the furnace of Furter and Hösli (cf. fig. 4), for example, is 20 cm. The movable heater can be opened and pushed back. The temperature of the lead dioxide is kept constant by a Philips "Miniwatt" valve, inserted as a resistance in the circuit. Before passing into the actual combustion tube the oxygen-stream goes through another electrically heated tube, filled with copper oxide. This is done so that organic impurities which may be present in the oxygen, will be burned

away. Oxygen is used in preference to air in this apparatus. Moreover, the combustion is carried out according to the usual method of operation of Pregl.

The micro-volumetric determination of nitrogen as gas (micro-Dumas method). The apparatus resembles very closely that used in the macro-method of determination, with the difference that all parts are constructed on a much smaller scale.

For the production of the current of air-free carbon dioxide, a carefully constructed Kipp's apparatus is used. The white marble, as pure as possible, must be free from cracks. It is broken up into small pieces, which are etched with hydrochloric acid and freed from enclosed air at the water-pump. The dilute acid (1 part concentrated acid to 1 part of water) is treated with marble before being placed in the Kipp's apparatus in order to remove any air from it. An apparatus prepared in this way produces air-free carbon dioxide in a short time. The connection with the combustion tube is made through a glass tap to which is fixed a piece of thermometer capillary tubing by means of rubber stoppers. The combustion tube, about 40 cm long and 10 mm wide, made of "Supremax" glass, narrows down at the end to a neck 3–3.5 mm wide. The tube is filled with a layer of wire-form copper oxide, 6 cm long, a 2 cm layer of pieces of copper wire (freshly reduced from copper oxide) which will be placed in the hottest part of the flame, and then a filling 5 cm long of wire-form copper oxide, the whole being kept in position by asbestos plugs at both ends.

For the analysis the tube is filled with coarsely powdered copper oxide containing the substance to be burnt.

Between the combustion tube and the azotometer a grooved tap is inserted by means of rubber tubing. Whilst the substance is being burnt the connection with the Kipp's apparatus is shut off, but the tube is connected to the azotometer. The combustion is carried on at such a rate that only one bubble of gas rises in the azotometer every two seconds. This speed can also be easily maintained when the carbon dioxide is being passed through, by means of the grooved tap.

The azotometer, which is filled with 50 per cent caustic potash, is composed essentially of a wide glass tube about 10 cm long, to which is fused a thick-walled capillary of which the capacity is about 1.8 cm³. It is graduated in tenths and hundredths of a cm³, and it is possible to estimate to one thousandth of a cm³.

For the analysis, 2–4 mg of the substance are weighed out, and mixed with coarsely powdered copper oxide. Liquids are placed in a capillary, containing a crystal of potassium chlorate, and drawn out, the tube being sealed during weighing, and being broken when introduced into the combustion tube. The micro-determination of nitrogen takes an hour at the most to carry out.

To correct for the capillary attraction of the caustic potash 2 per cent must be subtracted from the volume of nitrogen indicated by the azotometer.

The results obtained are as accurate as those given by the macro-method.

THE ELECTRICAL COMBUSTION FURNACE. The electrically heated furnace of Hösli (cf. fig. 5, and page 10) also offers great advantages in the determination of nitrogen. The long heater as well as the movable heater consist of two halves, the upper of which can be opened and pushed back. In this way, the combustion tube may be quickly cooled at the end of the analysis.

Derivation of chemical formulæ

(a) Empirical and Molecular Formulæ.

The basis of the derivation of every chemical formula is analysis. If all the constituent elements of an organic compound have been determined in the manner indicated above, and therefore the percentage amount of each element present

is known, the *empirical formula* can be obtained. This expresses the *ratio of atoms* of the elements in the compound concerned. This atomic ratio is obtained simply by dividing the percentage of each element by its atomic weight.

EXAMPLE 1: The analysis of a compound (benzene) gave 92.25 % C, and 7.75 % H. By dividing these percentages by the atomic weights of the respective elements we have

$$\text{for C, } \frac{92.25}{12} = 7.69; \quad \text{for H, } \frac{7.75}{1.008} = 7.69.$$

It follows that the *empirical formula of benzene* is $\text{C}_{2.22}\text{H}_{2.22}$, or, bringing the numbers of atoms to integers, C_1H_1 .

EXAMPLE 2: In the analysis of a substance (acetic acid), the following results were found: C, 40.0 %; H, 6.7 %; O, 53.3 %.

To obtain the empirical formula, the percentages are divided by the atomic weights of the corresponding atoms, giving

$$\text{for C, } \frac{40.0}{12} = 3.33; \quad \text{for H, } \frac{6.7}{1.008} = 6.65; \quad \text{for O, } \frac{53.3}{16} = 3.33.$$

The empirical formula of acetic acid is therefore



The empirical formula gives us, in the majority of cases, no detailed picture of the nature of the organic compound. Very often there exist other, indeed usually many more, *different* substances, which have the same empirical formula, but which differ in molecular size, structure, or arrangement of the various parts of the molecule in space. The next step to gain a clearer idea of the molecule than that given by the empirical formula alone is the determination of the molecular weight of the substance concerned.

The usual methods of determining molecular weights depending on the determination of vapour pressure or osmotic pressure (determination of elevation of the boiling point, or depression of the freezing point) may be used in organic chemistry. The reader must be assumed to be familiar with them.

By vapour density determinations, the molecular weight of benzene is found to be 77–80. It is seen that the simplest empirical formula for benzene, C_1H_1 , derived above, is not identical with the *molecular formula*, but must be multiplied by 6, in order to make it agree with it. The molecular formula of benzene is thus $(\text{C}_1\text{H}_1)_6$ or C_6H_6 (calculated molecular weight, 78).

In other cases, molecular weights determined by physical methods do not always give a true idea of the size of the molecule of the substance. If, for example, the molecular weight of acetic acid is determined by these methods, values considerably higher than the true ones (determined in other ways) are obtained. This anomaly is due to association of the acetic acid molecules, so that by the determination of vapour pressure and osmotic pressure it is not the molecular weight of the single molecules, but of aggregates of molecules (chiefly dimeric complexes) which is measured.

In this case the difficulty can usually be avoided by determining the molecular weight of a derivative of the substance, which is not associated. In the case of acetic acid ($\text{CH}_3\cdot\text{COOH}$), for example, the replacement of the functional hydrogen

atom by a hydrocarbon radical (alkyl group) gives an ester (e.g. $\text{CH}_3 \cdot \text{COOC}_2\text{H}_5$, ethyl acetate) which, unlike the parent substance, is not associated. From its lowering of vapour pressure the correct molecular weight of acetic acid can be found.

In other cases an insight into the molecular weight of a compound may be obtained by analysing one of its derivatives (salt, substitution product, etc.). It has already been said that acetic acid has the empirical formula $(\text{CH}_2\text{O})_x$; other acids, e.g. lactic acid, have the same empirical formula. The silver salts of the two acids, however, are quite different in composition. It is found that,

for silver acetate, C = 14.4 %, H = 1.8 %, O = 19.2 %, Ag = 64.6 %;

for silver lactate, C = 18.3 %, H = 2.5 %, O = 24.4 %, Ag = 54.8 %.

The empirical formulæ of the two salts are calculated in the usual way, when the following simplest formulæ are obtained:

for silver acetate, $\text{C}_{1.2}\text{H}_{1.8}\text{O}_{1.2}\text{Ag}_{0.6}$, or $\text{C}_2\text{H}_3\text{O}_2\text{Ag}$;

for silver lactate, $\text{C}_{1.53}\text{H}_{2.5}\text{O}_{1.53}\text{Ag}_{0.51}$, or $\text{C}_3\text{H}_5\text{O}_3\text{Ag}$.

From these results further conclusions can be drawn. On the one hand, the molecular formula of acetic acid cannot be less than $\text{C}_2\text{H}_4\text{O}_2$, and that of lactic acid cannot be less than $\text{C}_3\text{H}_6\text{O}_3$, since obviously neither molecule can contain less than *one* atom of silver. On the other hand the upper limits for the molecular formulæ of the two acids are not fixed by these observations. Silver acetate, for instance, could have the formula $\text{C}_4\text{H}_6\text{O}_4\text{Ag}_2$, and silver lactate, $\text{C}_6\text{H}_{10}\text{O}_6\text{Ag}_2$, and still agree with the analytical results. By such "chemical" methods of determining molecular weights it is therefore possible to fix the lower limit but never the upper limit of the molecular formula. The latter must be obtained by the "physical" methods of determining molecular weights (determination of vapour density or osmotic pressure). The results of these methods, however, are likewise no certain; although they give upper limits for the size of the molecule of the substance investigated, they do not exclude the possibility of smaller molecular weights. For, if the substance examined is one of which the molecules are associated, i.e. the molecules occur as aggregates, physical methods of determining molecular weights give an idea of the size of these aggregates, not that of the real chemical molecule. It was mentioned above that in the case of acetic acid, for example (and also lactic acid), which shows the phenomenon of association, the determination of osmotic pressure leads to a "molecular weight" which is greater than that corresponding to the actual formula $\text{C}_2\text{H}_4\text{O}_2$.

Both processes of molecular weight determination — the chemical and the physical — are thus complementary; the one gives the lower, the other the upper limit, and it is often only by the combined use of the two methods that the molecular formula of a compound can be obtained. The more complicated the structure of a substance, the greater are the difficulties in this connection. Thus, the "molecular weights" of many complex natural substances, such as proteins, starch, etc., obtained by the osmotic method are almost useless as an indication of their real molecular size, since there is no doubt that all these substances do not dissolve in water to give a true solution, but are colloidal. What is determined with such solutions is not the weight of the molecule, but the weight of these colloidal particles which may be composed of many molecules. On the other hand, it is also very difficult to obtain with certainty the lower limit for the molecular weight of such compounds, because it is rarely possible to prepare simple, or simple substituted, derivatives of them. That is why the molecular weights

of numerous important natural substances are not accurately known even to-day.

The most promising way to determine the magnitude of complex molecules is often to decompose them into smaller fragments, and to obtain from the nature of these products, an idea of the structure of the parent substance. The analytical results lose their significance if the molecular weight exceeds certain limits, because then the error in analysis is greater than the difference between closely related formulæ.

Some organic substances of very high molecular weight, and of known constitution, have been built up by synthesis, amongst them one of the composition $C_{220}H_{142}O_{58}N_4I_2$, of which the molecular weight is 4021. It resembles certain tannins. Amongst organic compounds of known constitution it appears to have the highest molecular weight (E. Fischer).

(b) **Structural or Constitutional Formulæ.**¹

The molecular formula is an empirical formula which gives, in most cases, no information about the mutual position and linking of the individual atoms in the molecule. In order to gain some insight into these properties it is necessary to derive a rational formula, or *structural formula*, for the organic compound concerned, which will provide a picture of the linkings of the various atoms in the molecule.

There is no general process for the derivation of the constitutional formulæ of organic compounds. The principle of the methods used is to identify in the compound in question, either by degradation, or transformation into derivatives, certain groups of atoms, e.g. $-CH_3$, or $-OH$, or $-NO_2$, which show the individual linkings of these atoms. If the whole substance is broken down into such partial groups, or if it can be transformed by a reaction which takes a definite, known course into a substance of which the structure is already known, it is usually possible to give its structure unequivocally.

The determination of structural formulæ is one of the most important problems confronting the organic chemist. They are, of course, not always equally easy to solve; the difficulties usually increase with increasing molecular weight and complexity of structure of the compound. The structure of very many naturally occurring substances is still unknown.

If, finally, on the basis of such degradation reactions, and analytical dissection, it is believed that the structure of a compound has been determined, it is sought, wherever possible, to confirm this derivation by synthesizing the substance. If this can be accomplished in such a way that it must lead, as far as can be foreseen, to a substance with the assumed constitution, this is a very valuable confirmation of the previous derivation.

In all later chapters, the derivation of organic constitutional formulæ will very often come before us. Here, in order to become acquainted with the principle of the method, the structural formulæ of only two very simple organic compounds, which have the same molecular formula, $C_2H_4O_2$, will be derived. The two substances are acetic acid and methyl formate (the methyl ester of formic acid).

In the determination of every constitutional formula the fact that elements combine only with definite numbers of other atoms must be taken into account. This is usually expressed by ascribing to the element concerned one or more

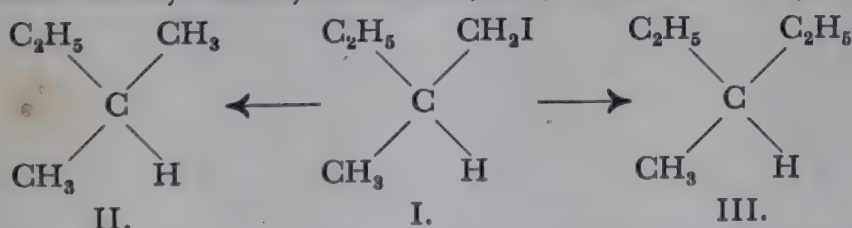
¹ On structural questions see also W. HÜCKEL, *Theoretische Grundlagen der Organischen Chemie* (2 vols.), Leipzig, (1940).

definite valencies. Thus, hydrogen, as is well known, is monovalent, oxygen usually divalent (in the oxonium salts it can have another valency, see p. 125), nitrogen tri- and pentavalent (and coordinately tetravalent), etc. In organic chemistry the valency of carbon plays a specially important part. It is almost always tetravalent, as is shown, for example, by the existence of the simple carbon compounds CH_4 , CCl_4 , CO_2 , CS_2 , etc. This element only departs from tetravalency in a few specially constituted compounds, which are characterized by their strong unsaturation, and often by great instability. They will be considered in a later part of this book. An exceptional case, that of carbon monoxide, CO , is already well known from inorganic chemistry.

A second important fact for the derivation of constitutional formulæ is that the four valencies of the carbon atom are of the same kind and are equivalent. This may be inferred from the fact that mono- and disubstitution products of methane, CH_4 , never occur in more than one form, whereas they obviously would if the four hydrogen atoms of methane were not equivalent, i.e. if they were linked by different types of valency forces.¹

Attempts have often been made to prove the equivalence of the carbon valencies. One method is to produce nitromethane, CH_3NO_2 in four different ways, in each of which, it may be presumed, a different hydrogen atom of methane is substituted; all such preparations are identical (Henry). This method, however, no longer provides conclusive evidence in favour of the statement, for we now know that a substituent entering a molecule often takes up another place from that occupied by the group which leaves (cf. the Walden Inversion). Experiments of the following kind are more conclusive:

If the four valencies of methane are attached to four different groups, the molecule produced is asymmetric and optically active (see p. 98). If two substituents are the same the asymmetry disappears and with it the optical activity. Such an optically active (asymmetric) methane derivative is the iodide, I. If the iodine atom in this compound is replaced by hydrogen, or, on the other hand, by the methyl group, inactive dimethyl-ethyl-methane, II, is obtained in the first case, and inactive methyl-diethyl-methane, III, in the second (Le Bel, F. Just):



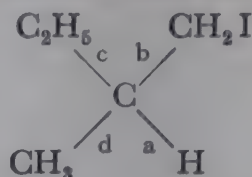
Since the hydrocarbons II and III are optically inactive, it follows that they

¹ This does not mean, however, that in substitution derivatives of methane, e.g., methyl chloride, CH_3Cl , the three hydrogen atoms and the chlorine atom claim exactly the same amounts of affinity of the carbon atom. On the contrary, it must be imagined that the affinity of a carbon atom can be distributed in different ways, so that one substituent may be endowed with more affinity than another essentially different one. The nature of the substituent is the deciding factor. If, however, in the methane molecule

$\begin{array}{c} \text{H (a)} \\ \diagdown \\ \text{C} \\ \diagup \\ \text{H (b)} \\ \diagdown \\ \text{H (c)} \\ \diagup \\ \text{H (d)} \end{array}$
 in one case the hydrogen atom (a), in another (b), or (c) is replaced by chlorine,

the same product is always formed, i.e. the chlorine atom is always linked to the carbon with the same amount of energy, no matter which hydrogen atom it replaces.

are symmetrical, the two CH_3 groups in II, and the two C_2H_5 groups in III being linked in the same way. Moreover, it may be concluded from this that in the methane derivative



the valencies b, c, and d are equivalent.

Let us now revert to the derivation of the structural formulæ of acetic acid and methyl formate, which both have the same composition and molecular formulæ.

ACETIC ACID. There is a hydroxyl group (OH) in the acetic acid molecule, since this can be substituted very easily and by many different methods by other atoms and groups. For example, the action of phosphorus pentachloride on acetic acid causes replacement of hydroxyl by chlorine. The new compound is acetyl chloride



We are therefore justified in writing the formula $[\text{C}_2\text{H}_3\text{O}]\text{OH}$ for acetic acid, and $[\text{C}_2\text{H}_3\text{O}]\text{ONa}$ for its sodium salt.

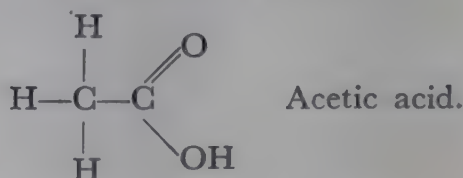
The three hydrogen atoms within the brackets must all be combined with the same carbon atom, since, if sodium acetate is distilled with dry sodium hydroxide, methane and sodium carbonate are formed:



Of the four hydrogen atoms in the methane, one came from the sodium hydroxide, and the other three from the acetyl radical, which therefore contains the group CH_3 . This result enables us to write the formula for acetic acid:



Thus its structural formula, which is to show the mutual linkings of the different atoms in the molecule, is derived. The above formula, whilst giving to carbon its constant valency of four, shows the arrangement of all the atoms unequivocally. If the individual valency bonds are shown in the formulation (which is not at all necessary, and is usually not done, since their distribution in the case of saturated carbon compounds is assumed to be known), the following scheme is obtained:



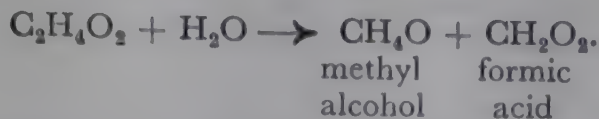
The further problem in the determination of the structure of acetic acid is to prepare the compound synthetically by a method of which the course is obvious, and can give a confirmation of the constitutional formula already derived. Of the many syntheses of acetic acid one is selected which is specially simple. Methyl sodium combines with dry carbon dioxide to give sodium acetate:



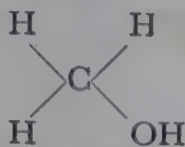
The reaction shows that all the hydrogen atoms in acetic acid which are not attached to oxygen in the hydroxyl group, must be attached to one, and all the oxygen must be attached to the other carbon atom, which was also the result obtained by breaking down the molecule.

METHYL FORMATE, $\text{C}_2\text{H}_4\text{O}_2$. This substance contains no hydroxyl since phosphorus pentachloride has no action upon it. On the other hand, heating with water

breaks the compound up into two parts, methyl alcohol and formic acid, and analysis shows that the fission has occurred with the taking up of one molecule of H_2O :

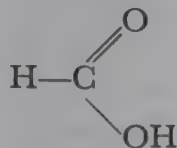


The constitution of methyl alcohol is definitely known if the tetravalency of carbon is maintained; it can only be represented by the formula



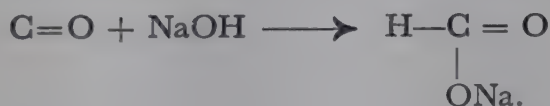
A confirmation of this is obtained by acting upon methyl alcohol with phosphorus pentachloride, when the hydroxyl group is replaced by chlorine, and methyl chloride, CH_3Cl , is formed.

In the second fission product of methyl formate, formic acid, there is also a OH -group; it can be replaced for example, by the $-\text{NH}_2$ radical. The formula of formic acid is therefore found to be

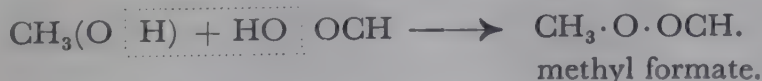


which also takes into account the tetravalency of carbon. Its sodium salt has the formula $\text{H} \cdot \text{CO}(\text{ONa})$.

In this case too, synthesis is called in to confirm the results of analysis. The sodium salt of formic acid is readily obtained if carbon monoxide is passed over heated sodium hydroxide. The reaction is the addition of NaOH to $\text{C}=\text{O}$, and its course is obvious:



Having thus derived the constitutional formulæ for both methyl alcohol, CH_3OH , and formic acid, $\text{H} \cdot \text{COOH}$, we can now consider how methyl formate, which is one molecule of H_2O poorer than the two together, is made up from the two fission products. Hydroxyl occurs in both methyl alcohol and formic acid, but is lacking in methyl formate. Hence the formula of the latter compound is obtained by splitting off water from the two hydroxyl groups:



The carrying out of the synthesis of methyl formate presents no practical difficulties. On heating formic acid with methyl alcohol, water and an equivalent amount of methyl formate are formed.

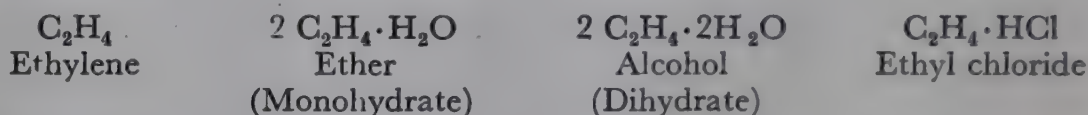
HISTORICAL REVIEW OF THE DEVELOPMENT OF THE FORMULATION OF ORGANIC COMPOUNDS

In the first decades of the XIXth century, when the number of known carbon compounds was increasing year by year, and their complicated structure

compared with that of inorganic compounds was recognized, and the phenomenon of isomerism (see page 23) was discovered, chemists were to begin with at a loss to explain and systematize these many new discoveries. The young and growing Organic Chemistry did not, however, escape the attention of the great investigators of the time, Berzelius, Dumas, and Liebig, and they, and others, sought to bring the newly discovered compounds into a system, and to arrange them according to definite principles. To this endeavour, the so-called *radical theory*, and its predecessor, the *etherin theory* owe their origin.¹

By "radicals" was originally understood atoms, or groups of atoms in compounds containing oxygen; the radical was the "residue" after oxygen had been subtracted. Later the concept was extended to include groups of atoms from substances not containing oxygen, so long as they fulfilled certain conditions. These were laid down as follows by Liebig: "The radical forms the non-variable constituent of a series of compounds, and can be replaced by other simple bodies; in its compounds with a simple body it can be removed and replaced by equivalents of other simple bodies." Berzelius called the radical an "element imitator".

The first organic radical was cyanogen, discovered by Gay-Lussac in 1815. The discovery, however, had less influence on the development of chemical theory than the investigations concerned with alcohol, ether, and ethyl chloride (hydrochloric ether), carried out about that time. Dumas drew attention to the fact that all these compounds could be regarded as addition compounds of ethylene, the so-called olefiant gas, C_2H_4 , with water and hydrogen chloride, as shown by the formulæ:



Berzelius called the radical, C_2H_4 , which formed the basis of all these derivatives, *etherin*, and drew attention to the analogy between its addition products and those of ammonia ($NH_3 \cdot H_2O$, $NH_3 \cdot HCl$, etc.).

Berzelius noted that the similarity between ammonia and etherin derivatives was only of a formal nature, and particularly that the characteristic property of the hydrate of ammonia, its basic power, was lacking in the hydrates of etherin (alcohol and ether).

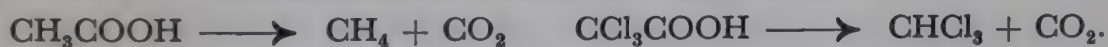
In spite of the strong adherence of Dumas to his etherin hypothesis it gradually lost ground, and the real radical theory gained acceptance. It received its first great impetus from a work by Liebig and Wöhler² on the benzoyl radical, in which they showed that oil of bitter almonds (benzaldehyde), benzoic acid, benzoyl chloride, benzoyl cyanide, benzamide, etc., contained a common oxygen-containing radical, C_7H_5O , which was transferred unchanged from one of these compounds to another. They gave it the name *benzoyl*. Here, therefore, was an actual "element imitator" in the form of a compound radical, leaving the question open as to whether this radical could exist in the free state uncombined with other atoms.

¹ See also E. HJELT, BERZELIUS, LIEBIG, DUMAS, *Ihre Stellung zur Radikaltheorie*, ed. by W. Herz, Stuttgart, (1907). — F. HENRICH, *Theorien der organischen Chemie*, Brunswick, (1924).

² See LIEBIG and WÖHLER, *Untersuchungen über die Radikale der Benzoesäure*, Leipzig, (1832). — J. LIEBIG, *Über die Konstitution der organischen Säuren*, Leipzig, (1838).

Shortly afterwards, Dumas and Péligot discovered the cinnamic acid or cinnamoyl radical, C_9H_7O — another group of atoms which showed properties similar to those of the benzoyl radical. At the end of the 1830's the arsenic-containing radical, *cacodyl*, $C_4H_{12}As_2$, was discovered by Bunsen. It acted as a divalent metal, and could be obtained in the free state. From the existence of this "free" cacodyl and its behaviour like a metal the radical theory received one of its greatest supports.

The ground on which the theory stood was, however, actually slipping away even at the time of Bunsen's discovery, and the theory could not be saved by the powerful defence of it put up by Berzelius. The view that the hypothesis of organic substances as being compounds of *invariable* electropositive and electronegative radicals was not sufficient to explain the multiplicity of their reactions, gained more and more ground. Dumas introduced the new point of view, proving, by means of excellent experimental investigations, that the hydrogen of many organic compounds could be replaced by chlorine by "substitution".¹ Thus, in ethylene, C_2H_4 , all the hydrogen atoms could be successively replaced by chlorine, and similarly one or more of the hydrogen atoms of naphthalene (Dumas, Laurent), and in acetic acid (CH_3COOH), one, two, or three hydrogen atoms could be replaced by chlorine ($CH_2Cl \cdot COOH$, $CHCl_2 \cdot COOH$, $CCl_3 \cdot COOH$) (Dumas). Particularly surprising, and contrary to established views, was the fact that the nature of the chlorine-substituted products did not vary very much from that of the original substance. Thus chlorinated naphthalene was very similar in properties to naphthalene itself; trichloroacetic acid possessed acidic properties like acetic acid and behaved in the same way as the latter in decomposition reactions. As an example, the reactions of the two acids with alkalis may be given. Acetic acid gives methane and carbon dioxide, whilst trichloroacetic acid gives trichloromethane (chloroform) and carbon dioxide.

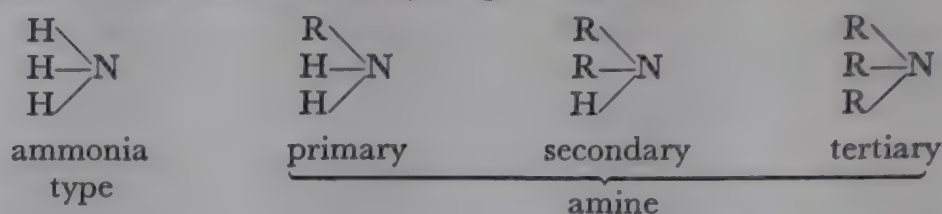


The objections and doubts which Berzelius raised against the "substitution theory" of Dumas (1834–1845) and which were based particularly on views, derived from inorganic chemistry, that a negative element like chlorine, bromine, or oxygen could not take the place of a positive one, hydrogen, rapidly lost significance in the face of the substitution processes now investigated with different classes of organic compounds. Laurent was the first to point out correctly that the chlorine in an organic compound is in a position to play a similar part to hydrogen in the original compound; the "type" of the compound (according to Dumas) suffered no change by such a substitution. In opposition to the views of Berzelius, Dumas stated, in his substitution theory, that it was not the electrochemical properties of the element which took the place of hydrogen in the organic molecule which determined to any extent the character of the new compound, but the way in which the atom was placed and linked in the new substance.

With this hypothesis, which assumed the existence of chemical "types" capable of substitution and modification, the way was prepared for a further development in chemical formulation, which led to the "*theory of types*".

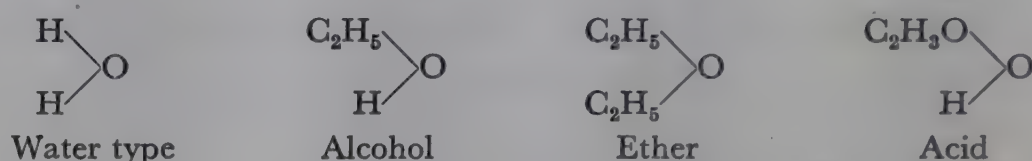
¹ See, for example, EDV. HJELT, *Der Streit über die Substitutionstheorie*, 1834–1845, Stuttgart, (1913).

The impetus to this was given by the discovery of the amines by Wurtz (1848) and their further investigation by A. W. Hofmann (1850). It was shown that these are basic, organic nitrogen compounds, which can be regarded as substitution products of ammonia in which one or more hydrogen atoms of ammonia have been substituted by organic radicals.

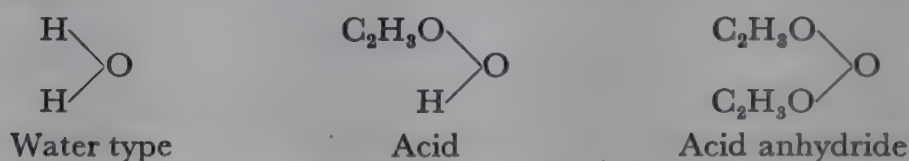


They are all based on the same parent substance, the ammonia type.

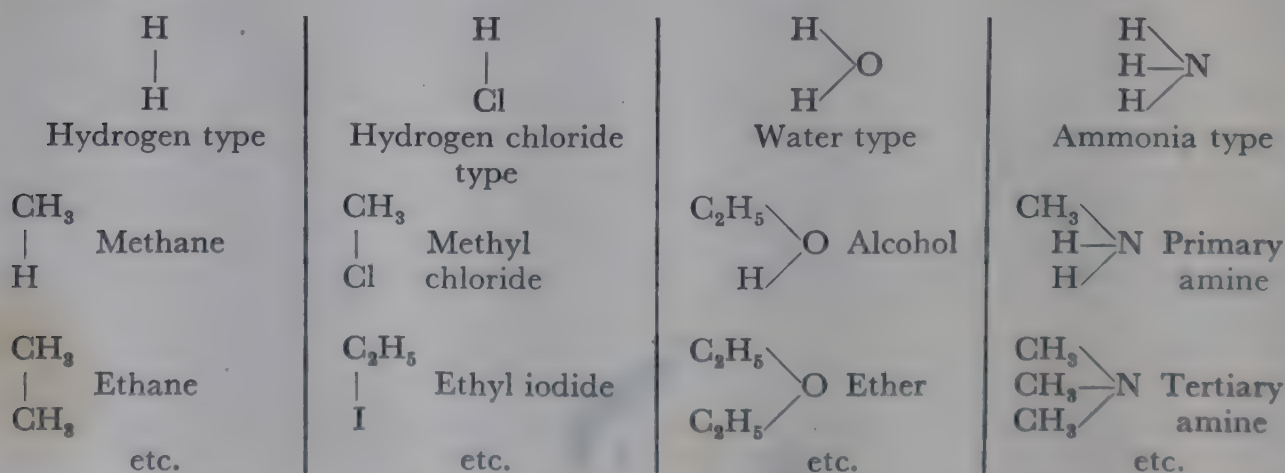
Almost at the same time, Williamson (1850) discovered a new method of preparing ether, by the interaction of potassium ethylate, $\text{C}_2\text{H}_5\text{OK}$, and ethyl iodide, $\text{C}_2\text{H}_5\text{I}$. In a similar way he obtained mixed ethers, $\text{R} \cdot \text{O} \cdot \text{R}'$ (R, R' are organic radicals). This discovery stirred him to seek a new explanation for the formulation of the ethers, and he considered their production and properties to be best explained if he regarded them as organic derivatives of water. On this "water type" the alcohols and the carboxylic acids could be explained quite simply.



An important confirmation of the usefulness of this hypothesis was the discovery in 1852 by Gerhardt of the "anhydrous acids", or acid anhydrides, which could be derived from the water type by replacement of both hydrogen atoms by acid radicals.



The further development of the theory of types to its final form is chiefly the work of Gerhardt. He added the hydrogen and hydrogen chloride types to the ammonia and water types, and these covered the majority of organic compounds then known.

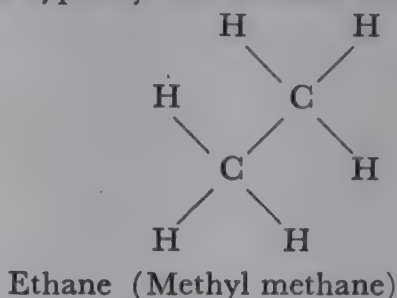
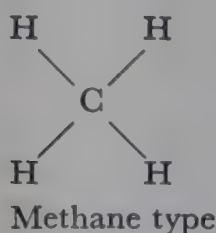


The theory of types was of great value in the systematization and further development of experimental chemical investigation. Actually it has never been

discarded, but only extended and modified, and has grown to what is now called *structural theory*. The important and decisive step was taken in this direction by Kekulé when he recognized the capacity of the elements to combine only with definite quantities of other atoms, and created the idea of "*valency*". He showed the tetravalency of the carbon atom from consideration of the structure of methane (1857). Simultaneously, and independently of him, Couper arrived at the tetravalency of carbon. Kekulé now added to Gerhardt's four types, that of

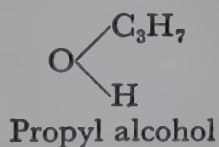
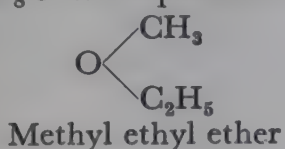
methane $\begin{array}{c} \text{H} \\ \diagup \\ \text{C} < \text{H} \\ \diagdown \\ \text{H} \end{array}$ and showed that carbon atoms could also link up with each

other, for which, in the simplest case, two valency units were required. In this way the bridge to modern structural theory was made; if the higher hydrocarbons are written as derived from the methane type by the Kekulé method,



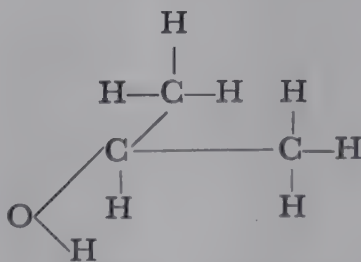
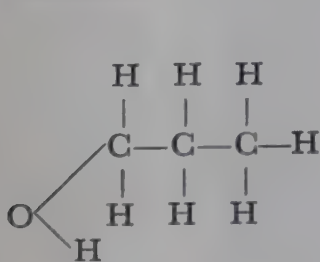
the formulation is obtained which is still in use to-day (cf. p. 15).

The putting forward of the *methane type* soon proved to be an extraordinarily fortunate method of attack. A number of types of isomerism for which the old theory of types was unable to offer any satisfactory explanation, were simply explained on this basis. Thus, according to the theory of types, only two compounds of the formula $\text{C}_3\text{H}_8\text{O}$ were predicted:



whilst actually three substances of this molecular formula existed.

The structural theory, on the other hand, basing the structure of the hydrocarbon residues on the methane type, predicted the existence of two isomeric propyl alcohols, the difference between which depends on the different structure of the C_3H_7 radicals.



Much later than this, facts, in particular, types of isomerism were discovered which even such structural formulæ could not explain. In order to be able to understand and explain them, the mutual bindings of the atoms as well as their arrangement in space within the molecule must be considered. The investigation of these steric properties is the task of *stereochemistry*, a branch of the subject which has been developed since about 1870. A special chapter will be devoted to the elements of this subject.

Section I. Hydrocarbons and compounds with one monovalent function

CHAPTER 2. HYDROCARBONS¹

The number of *aliphatic hydrocarbons* is exceedingly great. Their great number is a consequence of the capacity of the carbon atom to combine with other carbon atoms to form chains, a property which no other element possesses to the same degree, and which is shared, but only in a very incomplete way, by just a few other elements which are near carbon in the periodic system (e.g. silicon, nitrogen, phosphorus, and arsenic).

The upper limit to which the linking of carbon atoms extends is not known. A hydrocarbon has been synthesized which contains seventy carbon atoms directly linked with one another in its molecule, and there is nothing against the supposition that much longer carbon chains would be stable.

The special place which carbon occupies in this respect with regard to all other elements is partly due to its neutral electrical character, which is more favourable to the linking of atoms of the same kind in chains than is a definite electropositive or electronegative character. The Lewis-Langmuir theory gives a satisfactory explanation of the existence of the organic (i.e. homopolar, or covalent) carbon linkage, and is here assumed to be known.

The hydrocarbons are classified according to the proportion in which carbon and hydrogen occur in their structure. The hydrocarbons which are rich in hydrogen are called *saturated*. In them the greatest possible amount of hydrogen is combined with carbon. All other hydrocarbons, less rich in hydrogen, are said to be *unsaturated*. The unsaturated hydrocarbons are further sub-divided according to the proportion of carbon and hydrogen in them.

Saturated Hydrocarbons or Paraffins

The *saturated hydrocarbons* are known as paraffins (from *parum affinis*), on account of their small chemical reactivity. They are also sometimes known as the "limit" hydrocarbons, because in them the limit of saturation with respect to hydrogen is reached.

The derivation of the formulæ of the paraffin hydrocarbons depends on the tetravalency of carbon, a fact first expressed by Kekulé, and to-day generally accepted. Carbon differs from this normal state only in a few compounds of a special character. The following scheme, based on the consideration that in the combination of two carbon atoms one of the atoms must link one valency bond with one of the other atom, shows how the carbon chain of an aliphatic substance is built up:



¹ See also B. T. BROOKS, *The Chemistry of the Non-benzenoid Hydrocarbons and their simple derivatives*, New York, (1922).

The valency bonds not required for chain formation are, in the saturated aliphatic compounds, used up in linking other atoms. In the paraffin hydrocarbons these other atoms are hydrogen. It is easily seen that for the mutual linking of carbon atoms, $2n-2$ valencies are necessary. Since n carbon atoms have altogether $4n$ valency units, there remain for the attachment of hydrogen atoms in the saturated hydrocarbons $4n-(2n-2)$, or $2n+2$ valencies.

The paraffin hydrocarbons therefore correspond to the general formula C_nH_{2n+2} . The first members of the series are:

CH_4	Methane	$CH_3(CH_2)_4CH_3$	Hexane
$CH_3 \cdot CH_3$	Ethane	$CH_3(CH_2)_5CH_3$	Heptane
$CH_3 \cdot CH_2 \cdot CH_3$	Propane	$CH_3(CH_2)_6CH_3$	Octane
$CH_3 \cdot CH_2 \cdot CH_2 \cdot CH_3$	Butane	$CH_3(CH_2)_7CH_3$	Nonane
$CH_3 \cdot CH_2 \cdot CH_2 \cdot CH_2 \cdot CH_3$	Pentane	$CH_3(CH_2)_8CH_3$	Decane

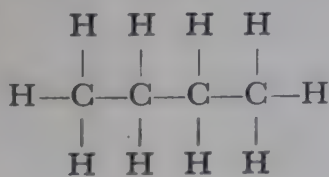
The first four paraffins have common names — methane, ethane, propane, and butane. From the fifth on, the Greek (or occasionally the Latin) numerals are used with the ending -ane, which generally characterizes the saturated hydrocarbons.

Two adjacent members of the paraffin series of hydrocarbons always differ by the group CH_2 . Compounds which have similar chemical and physical properties and which differ in composition by CH_2 , or some multiple of it, are called *homologous* compounds. The paraffin hydrocarbons form an *homologous series*. In general, chemical and physical properties do not vary suddenly, but gradually from member to member in an homologous series, so that a knowledge of the behaviour of a single member of the series enables conclusions to be drawn respecting the properties of lower and higher homologues.

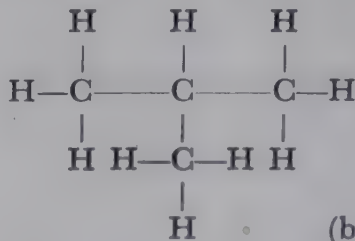
If a hydrogen atom is imagined to be removed from the paraffin hydrocarbons, there remain groups of atoms, or *radicals*, which have no separate existence, except possibly for a very short time (p. 152). From these radicals, by combination with other atoms or groups of atoms, derivatives are obtained. These are the *monovalent* derivatives of the hydrocarbons.

These radicals are of great importance in all the further work, and have special names. They are characterized by the ending -yl: CH_3 , *methyl*; C_2H_5 , *ethyl*; C_3H_7 , *propyl*; C_4H_9 , *butyl*; C_5H_{11} , *amyl*; C_6H_{13} , *hexyl*; C_7H_{15} , *heptyl*, etc. Generally they are referred to as *alkyl radicals* (or sometimes, alkyls). Their general formula is C_nH_{2n+1} . From "alkyl", and the ending -ane, which is used to characterize the saturated hydrocarbons, the word "*alkanes*" has been coined for the latter.

The first three members of the paraffin series occur only in one form. There are, however, two butanes, for which the formulæ (a) and (b) have been derived by synthesis.

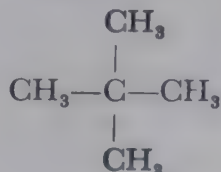
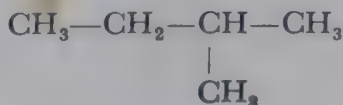


(a)



(b)

Pentane occurs in three different forms.



For the higher paraffins the number of possible forms increases very rapidly.

Substances which have the same chemical composition but different properties are called *isomers* or *isomerides*; the phenomenon is known as *isomerism*. Isomerism may be due either to different molecular size, when the term *polymerism* (polymeric substance) is used; or it depends on different arrangements of the individual atoms in the isomeric molecules and is then, generally, simply called *isomerism*.

The above-mentioned isomerism of butanes, pentanes, and higher paraffin hydrocarbons is a special case of *isomerism* which is known as *chain* (or *nucleus*) *isomerism*. The chain isomerism of the paraffin hydrocarbons depends on the capacity of the carbon atoms to link up together not only in straight chains, but also in branched chains. Those forms which possess a straight chain are called “*normal*”, e.g. *normal pentane* (abbreviated to *n*-pentane). The other pentanes are *isomers* of it and are called “*iso*”-forms.

Such formulæ give an idea of the mutual linkings between atoms in the molecule. They resolve the empirical formula into individual groups of atoms, and thus give a picture of the inner structure of the molecule. They are therefore *structural formulæ*. As the example of the butanes and pentanes shows, a knowledge of the empirical composition of an organic compound is not sufficient to give a clear idea of its nature; the structural formula gives a deeper insight into its make-up. Thus, in the investigation of an organic compound the first task is always the derivation of the structural formula, and the organic chemist writes his formulæ whenever possible in this way. The further development of the structural formula is the *stereo-formula* which seeks to express the position of atoms in space.

The carbon atoms in the paraffin hydrocarbons are not all equivalent; they have different numbers of hydrogen atoms attached to them (see, for instance, the formulæ of the isomeric pentanes). A carbon atom which is directly linked to only *one* other carbon atom, and which is therefore linked to three hydrogen atoms, is called a *primary* carbon atom. If it is combined with *two* other carbon atoms it is called *secondary*, and if with *three* other carbon atoms, *tertiary*. If all its four valencies are linked with other carbon atoms, it is called a *quaternary* carbon atom.

Methane occupies a special place — all the four valencies of the carbon atom are linked with hydrogen.

The Geneva Nomenclature.

It has already been said that the number of possible isomerides of the higher paraffins is very great. Calculation shows that 9 heptanes (C_7H_{16}), 18 octanes (C_8H_{18}), 35 nonanes (C_9H_{20}), 75 decanes ($C_{10}H_{22}$), 159 undecanes ($C_{11}H_{24}$), 1858 tetradecanes ($C_{14}H_{30}$), and 366,319 hydrocarbons of the formula $C_{20}H_{42}$ must exist. Of these, only comparatively few have been made synthetically at present; there is no doubt, however, that by the use of suitable methods of preparation all could be obtained.

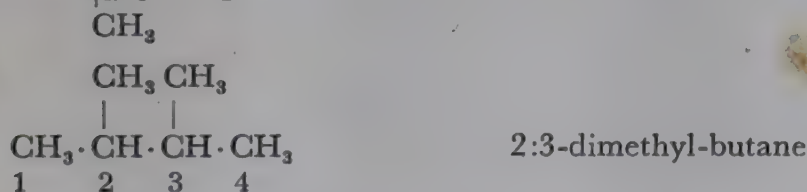
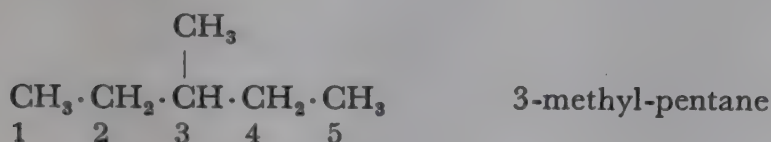
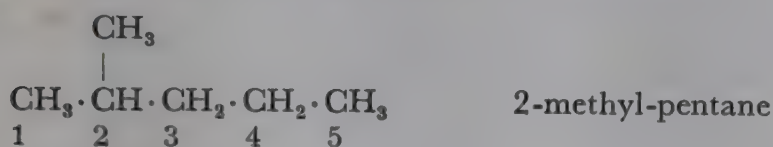
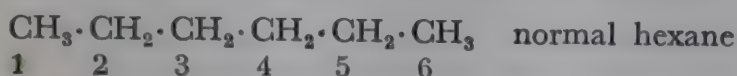
This multiplicity of paraffin hydrocarbons and their derivatives makes necessary a systematic nomenclature. In chemistry, two different methods of naming substances are in use. Either *common names*, derived from some property or other, or the occurrence of the substance, sometimes from the colour (e.g. Nile Blue), from the power to crystallize (e.g. Crystal Violet), from the plant from

which the substance is obtained (e.g. malvin, from the mallow), or from the substance from which the compound is made (e.g. fatty acids), are used; or a *rational* name is assigned, i.e. one which gives an accurate picture of the constitution of the substance concerned. The common names, which have many advantages, especially as regards brevity and clarity, are, in general, not satisfactory when it is necessary to distinguish between a large number of similarly constituted substances.

The *Geneva nomenclature* is a *rational* nomenclature for aliphatic compounds, resolved upon at Geneva in 1892 at a meeting of the International Chemical Congress, but it goes back in part to a suggestion made by A. W. Hofmann. The following standard principles are used in naming the paraffin hydrocarbons:

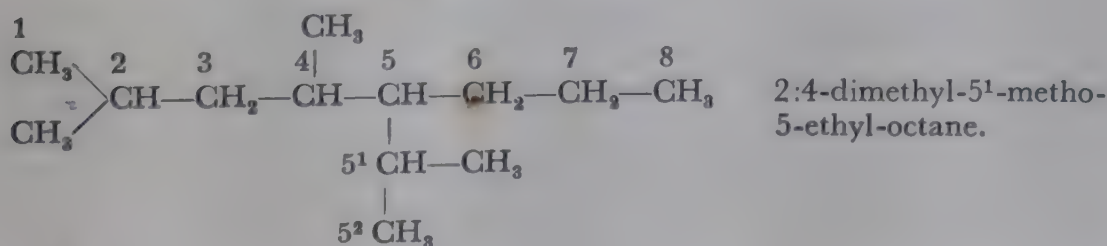
The basic name of the compound is chosen according to the longest normal carbon chain occurring in the molecule of the hydrocarbon. The carbon atoms of this chain are numbered from the left, and the position of the branch chain is indicated by the number of the carbon atom at which it branches off.

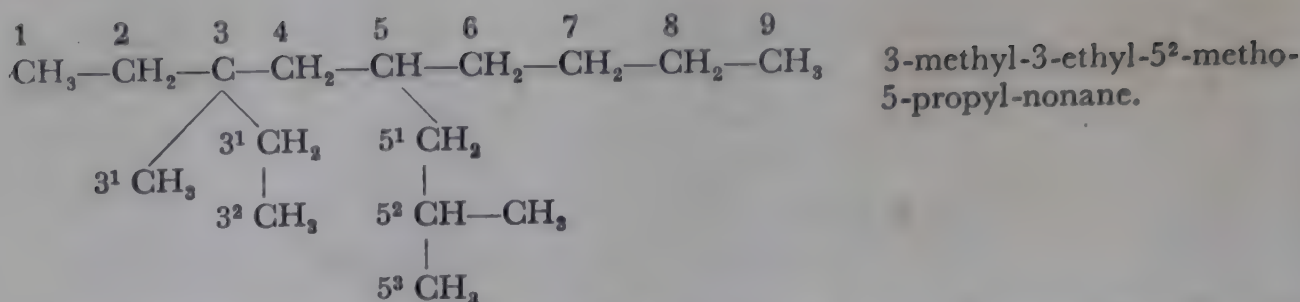
The names of the five possible hexanes are as follows:



The carbon atoms of a side-chain are numbered the same as the carbon atom of the principal chain at which the side-chain branches. In order to fix positions within the side-chain, indices are used. The numbering of the indices begins at the carbon atom of the side-chain next to that of the principal chain. If a further hydrocarbon residue is substituted in a side-chain, the names "metho", "propo" etc. are used for these instead of methyl, propyl, etc.

The names of some complex paraffins are given below:





Natural occurrence of paraffin hydrocarbons. The paraffins are widely distributed in nature. The lower members, particularly methane, and in much smaller quantities its near homologues, are found in gases issuing from the earth's crust. They form, for example, the chief constituents of natural gas, which is given off in oil-fields, and occasionally elsewhere. Gaseous mixtures rich in methane are also found in the neighbourhood of the potash deposits. See also p. 33.

Saturated hydrocarbons of medium and higher molecular weight are contained in almost inexhaustible quantities in certain kinds of mineral oil. The oil from Pennsylvania (U.S.A.) is especially rich in them, whilst that from the Caucasus (Baku) is poor in paraffins, consisting to a greater extent of hydrocarbons of another type. The Galician and Rumanian oils occupy an intermediate position and contain considerable quantities of paraffin hydrocarbons.

Mineral wax (ozokerite) is composed chiefly of a mixture of higher, solid paraffin hydrocarbons. It has been formed by the partial resinification and polymerization of the paraffin oil present in petroleum, and is found in large deposits in isolated places, e.g. Boryslaw in Galicia, in Rumania (Solontu, Moinesti, etc.), on the shores of Lake Baikal, at Tashkent, and on the Tscheleken Peninsula (Caspian Sea). It is used for similar purposes as the commercial paraffin. Purified and bleached mineral wax is called *ceresin*.

The lowest paraffin hydrocarbon, *methane*, is formed in nature by the bacterial decomposition of cellulose (methane fermentation); it is found in large and small fissures in coal-seams, and is produced in the destructive distillation of wood, peat, and coal. Coal gas therefore contains a large percentage of methane.

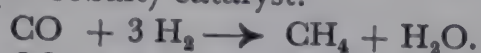
Methods of preparation of paraffin hydrocarbons. Although the paraffin hydrocarbons occur in some mineral oils to an almost unlimited extent, to prepare them in a state of purity preparative methods must be used in almost every instance, except perhaps for the first few members. The separation of hydrocarbon mixtures into their constituents is a very difficult task, which can only be carried out to some extent with the use of large quantities of material, and the loss of material is considerable. The physical and chemical properties of neighbouring members of the paraffin series are so similar that even by repeated fractional distillation or crystallization, mixtures of adjacent isomerides and homologues are often obtained.

1. Amongst the *methods of formation of methane*, those in which it is formed directly from its elements are of special theoretical interest. Methane can be obtained (according to Bone and Jerdan) from carbon and hydrogen heated to about 1200°. It is also formed, together with *acetylene*, and a little *ethane*, by passing an electric arc between carbon electrodes in an atmosphere of hydrogen (yield 1.25 per cent CH₄). In the latter case, the formation of methane is favoured by using hydrogen under pressure.

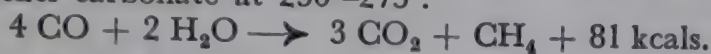


The building up of a chemical compound from its elements is called *total synthesis*. Total synthesis is of great importance in organic chemistry, for if it takes a course in which the various transformations of the intermediate compounds are perfectly clear, it is a valuable means of deciding the constitution of the compound which has been synthesized.

2. Methane is obtained more easily still by heating together carbon (soot) and hydrogen in the presence of finely divided nickel. The nickel acts as a catalyst, and activates the hydrogen. Sabatier and Senderens have shown¹ that carbon monoxide and carbon dioxide can be reduced by hydrogen at 250°–400° to methane, using a nickel (or cobalt) catalyst.



Methane can also be obtained, in theoretical yield, by passing carbon monoxide and steam over nickel carbonate at 250°–275°.

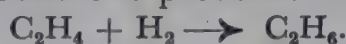


3. A third method of making methane and other paraffins from inorganic compounds is the decomposition of certain metallic carbides by water or acids. If iron, which contains iron carbide, is treated with acids, paraffin hydrocarbons are evolved. The formation of methane from aluminium carbide and water proceeds particularly smoothly (Moissan). It gives rather pure methane, and is a useful method of preparing this hydrocarbon, since aluminium carbide is now an article of commerce.



The extensive researches of Moissan have also shown the behaviour of other metallic carbides with water. Carbides of beryllium, thorium, uranium, and manganese all decompose water with liberation of methane, though the saturated hydrocarbon is mixed with unsaturated ones, particularly ethylene and acetylene.

4. Unsaturated hydrocarbons may be converted into saturated ones by addition of hydrogen. The reaction requires a high temperature if a catalyst is not used. It proceeds much more readily if the mixture of unsaturated hydrocarbon and hydrogen is passed over finely divided platinum or nickel powder (obtained by reduction of nickel oxide by hydrogen) at a high temperature (von Wilde, Sabatier and Senderens). Ethane is produced from ethylene and acetylene.



ethylene



acetylene

Since the individual unsaturated hydrocarbons, such as ethylene and acetylene are to-day easily accessible substances, their reduction to paraffins is important as a method of preparation.

5. Paraffins are formed, usually in good yield, by the reduction of the mono-halogen substitution products, the *alkyl halides*, $\text{C}_n\text{H}_{2n+1}\text{X}$ ($\text{X} = \text{Cl}, \text{Br}, \text{I}$).

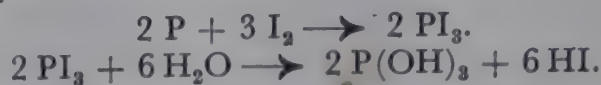


¹ See G. G. HENDERSON, *Catalysis in Industrial Chemistry*, New York, (1919). — P. SABATIER, *La catalyse en Chimie Organique*, 2nd ed., Paris, (1920). — S. J. GREEN, *Industrial Catalysis*, London, (1928). — C. ELLIS, *Hydrogenation of organic substances, including fats and fuels*, 3rd ed., London, (1930). — A. MITTASCH, *Über Katalyse und Katalysatoren in Chemie und Biologie*, Berlin, (1936). — V. N. IPATIEFF, *Catalytic reactions at high pressures and temperatures*, London, (1936). — H. ADKINS, *Reactions of hydrogen, with organic compounds over copper-chromium oxide and nickel catalysts*, Madison, (1937).

Sodium amalgam, sodium and alcohol, zinc and hydrochloric acid, and hydriodic acid (first used by Berthelot) may be used as reducing agents.



The effectiveness of hydriodic acid can be increased by the addition of red phosphorus, as this reacts with the iodine produced in the reaction, regenerating hydrogen iodide. The amount of hydriodic acid used up is re-formed so long as phosphorus is present.



A mixture of hydriodic acid and red phosphorus is often used in organic chemistry as a strong reducing agent.

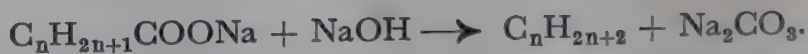
The zinc-copper couple, aluminium amalgam, or the zinc-palladium couple also reduce the alkyl halides very well; zinc dust in dilute alcoholic suspension may also be used.

6. A modification of the method described above is the reduction of alcohols instead of alkyl halides with hydriodic acid. The hydriodic acid first converts the alcohol into an alkyl halide, and then reduces the latter to a paraffin.

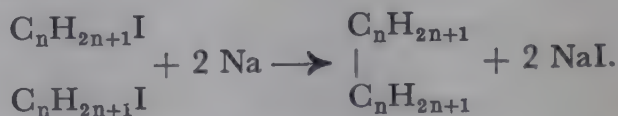
7. The reduction of fatty acids, i.e. derivatives of the paraffin hydrocarbons in which a hydrogen atom is replaced by the carboxyl group, COOH , takes place particularly easily with the higher acids and is important in the preparation of hydrocarbons of high molecular weight. The reducing agent is hydriodic acid and red phosphorus.



8. The method of Dumas is also one in which a carboxylic acid is converted into a hydrocarbon. The hydrocarbon produced, however, contains one carbon atom less than the acid from which it is prepared. The method is to heat the alkali metal or alkaline-earth metal salt of the carboxylic acid with sodium hydroxide, soda-lime, or barium hydroxide. The carboxyl group of the acid is thus split off as carbonate.



9. The Wurtz synthesis, by which halogen is removed from an alkyl halide by means of sodium, is important for the synthesis of paraffins. Two alkyl radicals unite to form a paraffin.



Unsaturated hydrocarbons of the ethylene series are often formed as by-products.

The work of different investigators (F. Krafft, J. U. Nef, F. S. Acree, P. Schorigin, H. H. Schlubach) has shown that alkylsodium compounds are formed as intermediate products in the Wurtz reaction; they react with the alkyl halides giving paraffin hydrocarbons.

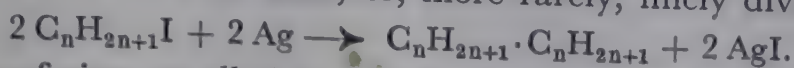


The course of this reaction is proved by the fact that when lithium acts on alkyl halides, alkyllithium compounds, which react fairly slowly with alkyl halides, can be isolated (K. Ziegler).

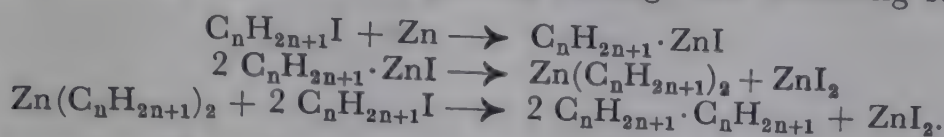
Alkyl sodium compounds, too, have recently been identified as intermediate products of these reactions.

The *Wurtz reaction* proceeds most easily with alkyl iodides, but the bromides and chlorides may also be used. It has been used for the synthesis of the hydrocarbons $C_{62}H_{126}$ (dohexacontane) and $C_{70}H_{142}$ (heptacontane), a hydrocarbon which contains one of the longest known normal carbon chains.

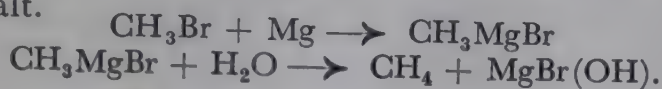
For the preparation of paraffins from alkyl halides finely divided (so-called molecular) silver can often be used, or, more rarely, finely divided copper.



The action of zinc on alkyl halides leads to similar final products (Frankland). As in the actual Wurtz reaction, organo-metallic compounds may occur as intermediate products, the reaction passing through the following steps:

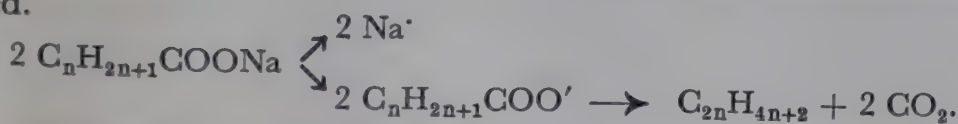


More important from the practical point of view is the synthesis of paraffins from alkyl halides and magnesium. This reaction, discovered by Grignard, gives in the first place an alkylmagnesium salt (Grignard compound), which, by the action of water is easily decomposed into the paraffin hydrocarbon and a basic magnesium salt.

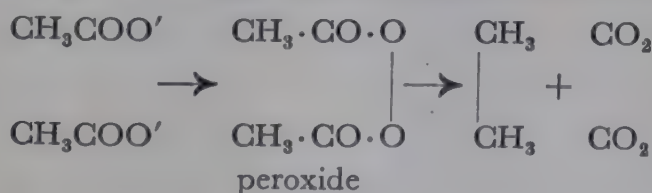


The reaction is usually carried out in ether solution.

10. A very elegant method of preparing saturated hydrocarbons is the *Kolbe synthesis*, in which fairly concentrated solutions of salts of the fatty acids are electrolysed. The metal ions travel to the cathode, the negative acid radical ions, $C_n H_{2n+1} COO'$ to the anode. Here the latter decompose into carbon dioxide and a paraffin which has twice as many carbon atoms as the alkyl radical of the acid electrolysed.

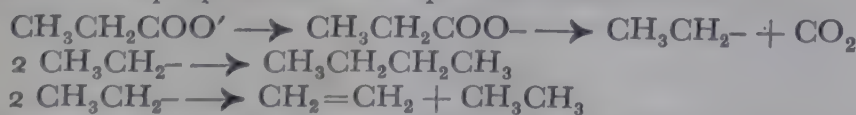


According to Fichter, the acid radical ions which travel to the anode are there oxidized to diacyl peroxides which then decompose into a paraffin hydrocarbon and carbon dioxide.



It is possible in the electrolysis of potassium caproate to isolate dicaproyl peroxide and caproic acid at the anode. Thus, it is proved that the formation of peroxides takes place in the Kolbe synthesis.

According to the views of other writers, e.g. K. Clusius, on electrolysis of the salts of fatty acids, alkyl radicals are formed first; these subsequently either dimerize into paraffin hydrocarbons or disproportionate into paraffin and olefin:



This explains why by-products are often formed in the Kolbe hydrocarbon synthesis, especially unsaturated hydrocarbons $C_n H_{2n}$ (ethylene hydrocarbons), and in small amounts also acid esters.

Physical properties of the paraffins.¹ The first four members of the paraffin series of hydrocarbons are gaseous at ordinary temperatures, those which follow, up to and including the sixteenth, are liquid at room temperature, those higher than this are solid.

The *boiling and melting points* are dependent on the size of the molecule. If the boiling and melting points of the normal paraffins are compared, the following regularities can be observed (see the table below):

		Boiling point	Boiling point differences	Melting point	Melting point differences	
					1st Series	2nd Series
Methane	CH ₄	—164°	71°	—184°		
Ethane	C ₂ H ₆	— 93.0°	48°	—171.4°		
Propane	C ₃ H ₈	— 45°	45.6°	—190°		
Butane	C ₄ H ₁₀	+ 0.6°	35.4°	—135°		
Pentane	C ₅ H ₁₂	+ 36°	32.7°	—129.7°		
Hexane	C ₆ H ₁₄	+ 68.7°	29.7°	— 95.5°		
Heptane	C ₇ H ₁₆	+ 98.4°	27.4°	— 90.8°		
Octane	C ₈ H ₁₈	+125.8°	24.9°	— 56.8°		
Nonane	C ₉ H ₂₀	+150.7°	22.3°	— 53.8°	21.8°	
Decane	C ₁₀ H ₂₂	+173°	22°	— 32°		5.5°
Undecane	C ₁₁ H ₂₄	+195°	20°	— 26.5°	14.5°	
Dodecane	C ₁₂ H ₂₆	+215°	19°	— 12°		5.8°
Tridecane	C ₁₃ H ₂₈	+234°	18°	— 6.2°	11.2°	
Tetradecane	C ₁₄ H ₃₀	+252°	18°	+ 5.0°		5.0°
Pentadecane	C ₁₅ H ₃₂	+270°	17°	+ 10°	8.0°	
Hexadecane	C ₁₆ H ₃₄	+287°	16°	+ 18°		4.5°
Heptadecane	C ₁₇ H ₃₆	+303°	14°	+ 22.5°	5.5°	
Octadecane	C ₁₈ H ₃₈	+317°	13°	+ 28°		4.0°
Nonadecane	C ₁₉ H ₄₀	+330°		+ 32°	5.0°	
Eicosane	C ₂₀ H ₄₂	+208°	at 15 mm pressure	+ 37°		3.4°
Heneicosane	C ₂₁ H ₄₄	+219°		+ 40.4°	4.0°	
Docosane	C ₂₂ H ₄₆	+230°		+ 44.4°		3.3°
Tricosane	C ₂₃ H ₄₈	+240°		+ 47.7°	3.4°	
Tetracosane	C ₂₄ H ₅₀	+250°		+ 51.1°		2.9°
Pentacosane	C ₂₅ H ₅₂	+259°		+ 54°		
Hentriacontane	C ₃₁ H ₆₄	+312°		+ 68°		
Dotriacontane	C ₃₂ H ₆₆	+320°		+ 70°		
Pentatriacontane	C ₃₅ H ₇₂	+344°		+ 74.6°		
Pentacontane	C ₅₀ H ₁₀₂			91.9°–92.3°		
Hexacontane	C ₆₀ H ₁₂₂			98.5°–99.3°		
Heptacontane	C ₇₀ H ₁₄₂			105°–105.5°		

1. The *boiling point* rises with increasing molecular weight. The difference in the boiling point of two adjacent members, however, becomes smaller as the homologous series is ascended. Thus, the introduction of a new CH₂ group has a proportionately smaller effect, the higher the hydrocarbon stands in the homologous series.

2. The *melting point* increases slowly with increasing molecular weight. In

¹ GUSTAV EGLOFF, *Physical Constants of Hydrocarbons*, New York, (1940).

this case too, the difference between the melting points of two adjacent members, becomes, in general, smaller the higher the two hydrocarbons are in the homologous series. In this connection there is a peculiar fact: up to the twenty-fourth member large and small melting point differences alternate. In other words, with regard to melting points, the homologous series of normal paraffins can be divided into *two sub-series*; one comprises those compounds with an even number of carbon atoms in the molecule, the other, those with an odd number. In the two series the melting point differences for two adjacent members become smaller as the series is ascended, but the values for the two series are different. Hydrocarbons with an even number of carbon atoms melt at a relatively higher temperature than those with an odd number.

Similar relationships are found in many other homologous series, for example the series of carboxylic acids. The separation into those with even and odd numbers of carbon atoms respectively, can be made not only in connection with melting point, but with many other properties, such as their physiological action, dissociation constants, etc. The oscillation of properties within the homologous series must be due to a special molecular structure of the even and odd members.

If the boiling points of structurally isomeric paraffins are compared it is found that the normal compound always has the highest boiling point. The other isomerides boil at a lower temperature, and, in general, the boiling point decreases with increasing branching of the chain.

Thus, for example, the five hexanes have the following boiling points:

$\text{CH}_3 \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH}_3$ *n*-hexane, b.p. 68.75°.

$\begin{array}{c} \text{CH}_3 \cdot \text{CH}_2 \cdot \text{CH} \cdot \text{CH}_2 \cdot \text{CH}_3 \\ | \\ \text{CH}_3 \end{array}$ 3-methyl-pentane, b.p. 63.30°.

$\begin{array}{c} \text{CH}_3 \cdot \text{CH} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH}_3 \\ | \\ \text{CH}_3 \end{array}$ 2-methyl-pentane, b.p. 60.30°.

$\begin{array}{c} \text{CH}_3 \cdot \text{CH} \cdot \text{CH} \cdot \text{CH}_3 \\ | \quad | \\ \text{CH}_3 \quad \text{CH}_3 \end{array}$ 2:3-dimethyl-butane, b.p. 58.05°.

$\begin{array}{c} \text{CH}_3 \\ | \\ \text{CH}_3 \cdot \text{C} \cdot \text{CH}_2 \cdot \text{CH}_3 \\ | \\ \text{CH}_3 \end{array}$ 2:2-dimethyl-butane, b.p. 49.70°.

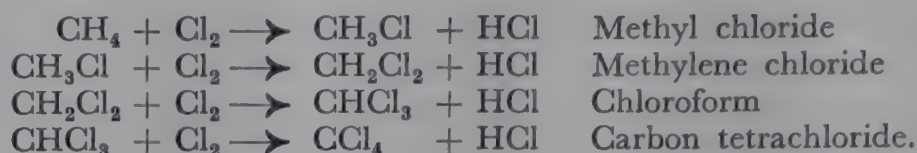
Amongst the other physical properties of the paraffin hydrocarbons it must be mentioned that the gaseous members (methane and ethane) are odourless, the easily volatile, lower paraffins have a petrol-like smell, whilst the highest, on account of their low volatility, have no smell.

The specific gravity increases slowly with the molecular weight; in the case of the higher members with the normal structure, the value has been shown by F. Krafft to be almost constant (about 0.776–0.780).

All the paraffins are only exceedingly slightly soluble in water.

Chemical properties of the saturated hydrocarbons¹. The paraffins have formerly been regarded as substances which exhibit a particularly small tendency to enter into chemical reaction. The generalization must not, however, be pushed too far. In the course of time many methods have been discovered by which the decomposition of paraffin hydrocarbons can be carried out surprisingly easily. However, the products of reaction are seldom homogeneous.

Of the *halogens*, chlorine and bromine replace the hydrogen atoms of paraffins even at ordinary temperatures. In methane all four hydrogen atoms can be successively replaced by chlorine:



Such a process is called *substitution*. It is not easy to carry out the chlorination of methane in such a way that the reaction can be stopped at any desired stage of the chlorination, and mixtures of the different chlorination products are obtained.

In the case of the higher normal saturated hydrocarbons, the halogens often react (according to Victor Meyer) so that the bromine or chlorine atoms entering attach themselves to adjacent carbon atoms:



As a rule the halogenation of paraffins can be greatly accelerated by the use of catalysts. Traces of iodine, or exposure to light act in this way. In sunlight chlorine and methane react so vigorously that the hydrocarbon is decomposed explosively with formation of carbon:



Iodine does not substitute directly in saturated hydrocarbons.

The middle and higher paraffins are sulphonated by *fuming sulphuric acid*, i.e. a hydrogen atom is replaced by the sulphonic acid radical, $-\text{SO}_3\text{H}$. The lower, gaseous members are more stable, but dissolve slowly in sulphuric acid.

The behaviour of the paraffins towards *nitric acid* is different. If they contain a tertiary carbon atom (which is usually specially easily attacked), they can be oxidized by concentrated nitric acid to carbon dioxide and lower fatty acids (Markovnikov, Poné). Normal hydrocarbons are more stable. They are converted into nitro-derivatives, which, according to Konovalov, Worstall, and others, are also obtained from some paraffins by treating these with dilute nitric acid at high temperatures, or, according to Urbanski and Slon by the action of gaseous N_2O_4 on the heated vapours of the hydrocarbons (See further p. 138).

Of special interest are the experiments on the *oxidation of the paraffins* to fatty acids, because this is closely connected with the problem of producing fats artificially from petroleum. Although it appeared at first that a controlled, partial oxidation involved very considerable difficulties, and that oxidation with chromic acid (Gill and Meusel), or with nitric acid (Willstätter, Fillipuzzi and Meusel, Pouchet) led chiefly to the formation of lower, liquid fatty acids, later work has

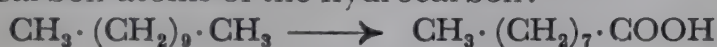
¹ B. T. BROOKS, *The Chemistry of the Non-Benzenoid Hydrocarbons and their simple Derivatives*, New York, (1922). — G. EGLOFF, *Reactions of Pure Hydrocarbons*, New York, (1937). — G. EGLOFF, G. HULLA, V. I. KOMAREWSKY, *Isomerization of Pure Hydrocarbons*, New York, (1944).

revealed the fact that the saturated hydrocarbons are surprisingly easily oxidized. If ordinary commercial paraffin, or individual higher paraffins are treated with oxygen, air, or even by waste gases which contain only a little oxygen, at a temperature of 100–160°, higher fatty acids are produced (R. von Stepsky, Gray, Bergmann, Kelber, A. Grün). Whilst various workers recommend the addition of catalysts to accelerate the reaction (metals, metal oxides, metal salts, fatty acids), according to others these are unnecessary or inactive. These methods of oxidation are at present being extensively investigated in industry.¹

If the oxidation is not carried too far, medium and higher fatty acids are obtained in this way from commercial paraffin. Among the acids found were capric acid $C_{10}H_{20}O_2$, lauric acid $C_{12}H_{24}O_2$, myristic acid $C_{14}H_{28}O_2$, palmitic acid $C_{16}H_{32}O_2$, stearic acid $C_{18}H_{36}O_2$, behenic acid $C_{22}H_{44}O_2$, and lignoceric acid $C_{24}H_{48}O_2$. These are the same acids that also occur in natural fats. However, when paraffin is decomposed by oxidation, monocarboxylic acids with odd numbers of C-atoms which seldom occur in natural fats are also produced.

In addition to the simple acids, hydroxy-acids and unsaturated acids are formed as further oxidation products. A. Grün also found higher alcohols and carbonyl compounds of unknown nature amongst the products.

Other processes for oxidizing paraffin use nitrogen dioxide as the oxidizing agent (Ch. Gränacher) or other nitrogen oxides. The products here are again hydroxy-acids and higher fatty acids from among which one of the formula $C_{21}H_{43}COOH$ has been isolated. Using a homogeneous paraffin hydrocarbon, undecane, $C_{11}H_{24}$, an insight into the course of the reaction was obtained. Undecane undergoes degradation by the action of nitrogen dioxide, giving the acid $C_9H_{17}COOH$ (nonylic acid, pelargonic acid), so that the oxidizing agent has removed two carbon atoms of the hydrocarbon:



INDIVIDUAL MEMBERS OF THE PARAFFIN SERIES OF HYDROCARBONS

Methane. Methane is an important constituent of many natural gases. It occurs in those gases which arise from the interior of the earth in the borings in oil-fields. The sources of natural gas sometimes do not become exhausted for quite a considerable period. For example, the Holy Fire of Baku has been maintained since ancient times by streams of natural gas. The gas contained in fissures in coal-seams contains about 80–90 per cent of methane. It is produced in this case from the organic constituents of the coal by a kind of dry distillation. The air of coal-mines always contains methane (3.5–7.5 per cent). This gas mixture, which explodes violently on applying a flame has received the name “fire-damp”.

Methane is being formed in nature continuously by bacterial decomposition of cellulose — the *methane fermentation* of cellulose. In marshes, on the bottoms of which bacteria act upon cellulose, the gas rises to the surface of the water. This fact accounts for the name “marsh-gas”. Omelianski, during the course of his pioneer work on cellulose fermentation processes, also investigated methane fermentation more closely, and showed that in addition to methane, fatty acids, and carbon dioxide were produced as further decomposition products. The

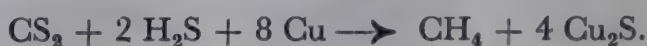
¹ See also WITTKA, *Gewinnung der höheren Fettsäuren durch Oxydation der Kohlenwasserstoffe* Leipzig, (1940).

decomposition of cellulose in the paunches of ruminants is also a methane fermentation. This explains the fact that the respired air of animals that have eaten cellulose contains the hydrocarbon, which is also present in the intestinal gases and blood gases of animals and man.

"Wood-gas", which is produced by the destructive distillation of wood, contains large quantities of the hydrocarbon, as do also the gases obtained by heating peat or coal (coal-gas).

For the *preparation of methane*, one of the general methods of preparation of the paraffin hydrocarbons described above may be used, as, for example, the decomposition of methylmagnesium iodide with water, heating a mixture of sodium acetate and soda-lime, reduction of methyl iodide with the zinc-copper couple, or the action of water on aluminium carbide.

The synthesis of methane by passing a mixture of carbon disulphide vapour and hydrogen sulphide over heated copper is of historical interest, being the first synthesis of the hydrocarbon (Berthelot, 1856):



Recently, methods of preparing methane have been patented which depend on passing higher hydrocarbons, together with hydrogen, over contact catalysts (e.g. nickel).

Methane is colourless and odourless, and burns with a faintly luminous flame. It is very slightly soluble in water, but appears, from thermochemical data, to form a hydrate containing six molecules of water.

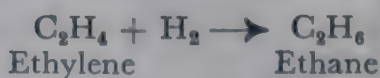
A mixture of methane and oxygen or air explodes violently on ignition. However, the combustion temperature of methane is very high. It is much more difficult to burn than hydrogen and all other hydrocarbons. This behaviour is a difficulty in the elementary analysis of organic substances which split off methane during the combustion, and particularly affects the determination of nitrogen by the Dumas method, since, if the heating is not sufficient, methane leaves the tube unoxidized. This property of being difficultly combustible even when mixed with air and in the presence of heated platinum is made use of in gas analysis to determine methane in the presence of other hydrocarbons.

Ethane. Ethane occurs dissolved in mineral oil and is evolved in the gaseous state when the oil comes to the surface. The gases evolved from oil-bearing layers also often contain considerable quantities of ethane.

It is a colourless, odourless gas, which burns with a faintly luminous flame. It is slightly soluble in water, forming with it a hydrate, $\text{C}_2\text{H}_6 \cdot 7 \text{H}_2\text{O}$. Ethane is somewhat more soluble in alcohol than in water.

Any of the general methods described above may be used for the *preparation* of ethane, for example, the electrolysis of potassium acetate, or the reduction of ethyl iodide with hydriodic acid or the zinc-copper couple.

Technically, ethane is made by the method of Sabatier and Senderens from ethylene and hydrogen, the two gases being passed over finely divided nickel as a catalyst. Ethylene itself is easily obtained from alcohol by dehydration.



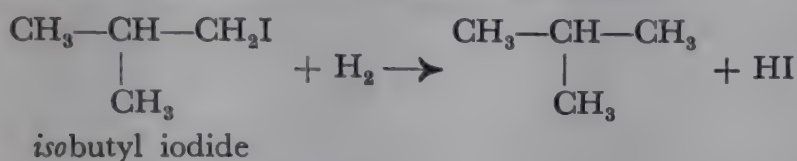
Ethane is used as a fuel gas in those places where it comes from the earth in large quantities. In addition it has a limited application as a gas in refrigerators.

Propane can be prepared synthetically from propyl iodide or isopropyl iodide by reduction with the zinc-copper couple. It is a gas which burns with a more luminous flame than ethane. Propane is found in large quantities in natural gases, in cracking gases which are obtained from mineral oil, in gases from petrol refining, and in those produced in the Fischer-Tropsch synthesis of petrol (q.v.). This hydrocarbon has become the starting material for numerous syntheses which are carried out industrially on a large scale. Chlorination leads to 1-chloro-, 2-chloro-, 1:2-dichloro-, and 1:3-dichloropropane (cf. under halogen derivatives); nitration gives nitroparaffins, starting materials for amines. Dehydrogenation of propane yields propylene (q.v.) from which allyl chloride, glycerol, isopropyl alcohol, etc. are manufactured. Furthermore, branched-chain hydrocarbons (2-methyl-pentane, 2:3-dimethyl-butane etc.) are produced by polymerization of propane and propylene and are used as additions to aviation spirit (increase of the octane number, cf. page 40).

Butanes. There are two butanes, *normal butane*, and *isobutane*, or *methyl-propane*. Both occur in mineral oil. Their constitution is made clear by synthesis.

n-Butane can be synthesized from ethyl iodide and sodium by the Wurtz method: $\text{CH}_3\text{CH}_2\text{I} + 2 \text{Na} + \text{ICH}_2\text{CH}_3 \rightarrow \text{CH}_3 \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH}_3 + 2 \text{NaI}$.

Isobutane is formed by the reduction of *isobutyl iodide*:



Pentanes, hexanes, heptanes. Three structural isomerides of pentane, five of hexane and nine of heptane are possible, and have been prepared. The formulæ of the heptanes are:

$\text{CH}_3 \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH}_3$ normal heptane, b.p. 98.3°.

$\text{CH}_3 \cdot \text{CH} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH}_3$ 2-methyl-hexane, b.p. 90.0°.

$\begin{array}{c} \text{CH}_3 \\ | \\ \text{CH}_3 \cdot \text{CH}_2 \cdot \text{CH} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH}_3 \\ | \\ \text{CH}_3 \end{array}$ 3-methyl-hexane, b.p. 91.8°.

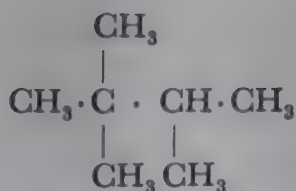
$\begin{array}{c} \text{CH}_3 \\ | \\ \text{CH}_3 \cdot \text{C} \cdot \text{CH}_2 \cdot \text{CH}_2 \cdot \text{CH}_3 \\ | \\ \text{CH}_3 \end{array}$ 2:2-dimethyl-pentane, b.p. 78.9°.

$\begin{array}{c} \text{CH}_3 \\ | \\ \text{CH}_3 \cdot \text{CH}_2 \cdot \text{C} \cdot \text{CH}_2 \cdot \text{CH}_3 \\ | \\ \text{CH}_3 \end{array}$ 3:3-dimethyl-pentane, b.p. 86.0°.

$\begin{array}{c} \text{CH}_3 \quad \text{CH}_3 \\ | \quad | \\ \text{CH}_3 \cdot \text{CH} \cdot \text{CH} \cdot \text{CH}_2 \cdot \text{CH}_3 \end{array}$ 2:3-dimethyl-pentane, b.p. 89.7°.

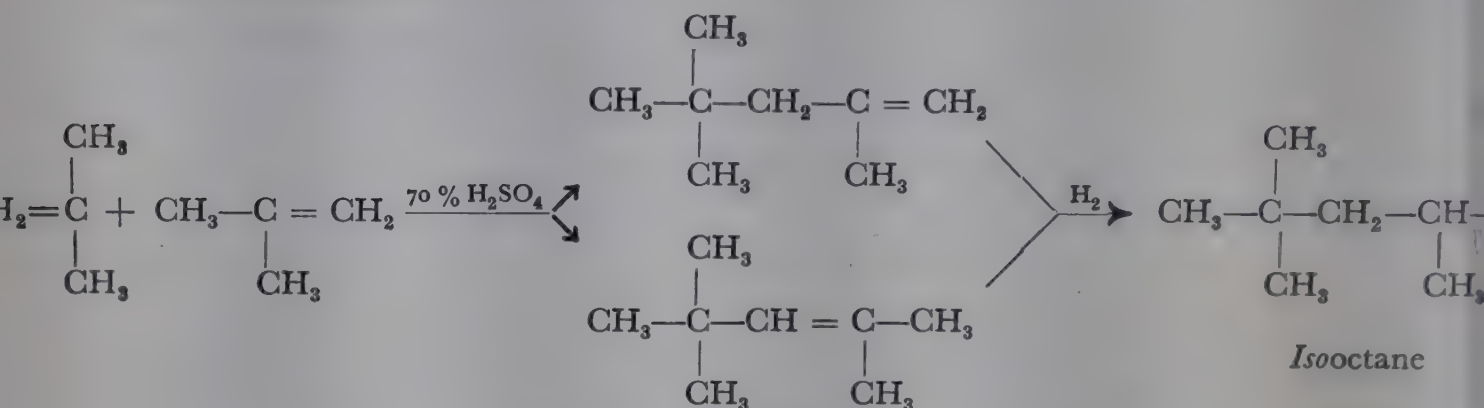
$\begin{array}{c} \text{CH}_3 \quad \text{CH}_3 \\ | \quad | \\ \text{CH}_3 \cdot \text{CH} \cdot \text{CH}_2 \cdot \text{CH} \cdot \text{CH}_3 \end{array}$ 2:4-dimethyl-pentane, b.p. 80.8°.

$\begin{array}{c} \text{CH}_3 \quad \text{CH}_3 \\ | \quad | \\ \text{CH}_3 \cdot \text{CH}_2 \cdot \text{CH} \cdot \text{CH}_2 \cdot \text{CH}_3 \\ | \\ \text{CH}_2 \\ | \\ \text{CH}_3 \end{array}$ 3-ethyl-pentane, b.p. 93.3°.

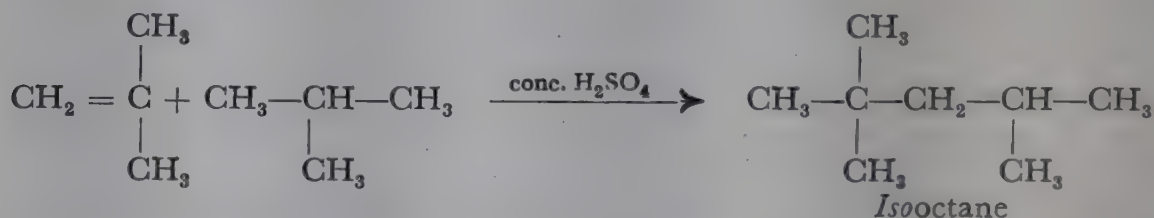


2:2:3-trimethyl-butane, b.p. 80.9°.

Among the **octanes**, 2:2:4-trimethylpentane, usually simply called *isooctane*, is a very important technical product. It serves, as we shall see in the section on mineral oil, as a standard in the determination of the resistance to knocking of motor fuels (octane number). Owing to its excellent resistance to knocking it has lately been produced in enormous quantities by the mineral oil industry and is used as an admixture for high-grade petrols, especially aviation spirit. In its preparation the *isobutylene* of cracking gases is used as a starting material. The *isobutylene* is first dimerized with moderately concentrated sulphuric acid, when a mixture of two *isooctylenes*, only differing in the position of the double bond, is obtained. Both are transformed into the desired *isooctane* when subsequently hydrogenated:



A second particularly elegant process has lately rapidly come into favour ("alkylation process"). It is based on the interesting observation that under suitable conditions, e.g. in the presence of concentrated sulphuric acid, direct addition of *isobutylene* on to *isobutane* with formation of *isooctane* takes place:



As the mineral oil industry also produces considerable quantities of *isobutane*, which formerly were only used for heating purposes, the advantages of the latter method are obvious.

Higher paraffin hydrocarbons. These are found in the less volatile fractions of mineral oil. The saturated hydrocarbons $\text{C}_{24}\text{H}_{50}$, $\text{C}_{31}\text{H}_{64}$, $\text{C}_{32}\text{H}_{66}$, $\text{C}_{34}\text{H}_{70}$, $\text{C}_{35}\text{H}_{72}$ have been isolated from commercial paraffin, and F. Krafft obtained eighteen saturated normal hydrocarbons, the members of the series from $\text{C}_{19}\text{H}_{40}$ to $\text{C}_{36}\text{H}_{74}$, by fractional distillation of paraffin from lignite. He identified them by comparing them with the hydrocarbons synthesized by reduction of acids, ketones, and alcohols. The normal structure of all these paraffins followed from the fact that all the starting materials (acids, ketones, and alcohols) were normal.

Higher paraffin hydrocarbons are often met with in nature. Thus, *heptacosane* $\text{C}_{27}\text{H}_{56}$, and *hentriacontane* $\text{C}_{31}\text{H}_{64}$, are found in bees wax, and in smaller quantities in American tobacco. The second of these hydrocarbons is also found in green leaves. Heptacosane has been found in soot and sperm.

The hydrocarbon dohexacontane $C_{62}H_{126}$, is of theoretical interest. It was obtained by Hell and Hägele synthetically from myricyl iodide by fusing it with sodium:



(According to Gascard, myricyl iodide should have 31 carbon atoms, not 30 as previously thought.)

Dohexacontane is a stable crystalline compound, of melting point 102° . Carbon chains of such length are therefore not inclined to decompose, and it can be predicted that the preparation of compounds containing still longer chains is possible.

Recently, by the action of sodium on decamethylene bromide, $Br(CH_2)_{10}Br$, (Wurtz reaction) various higher paraffins, such as $C_{20}H_{42}$, $C_{30}H_{62}$, $C_{40}H_{82}$, etc., with straight carbon chains, one of which contained as many as 70 carbon atoms, were obtained. This heptacontane melts at 105° , crystallizes well, and is difficultly soluble in organic solvents.

MINERAL OIL¹

OCCURRENCE. Mineral oil is found in many places, in greater or less quantity. The most important oil-fields are those in North America, particularly in those States through which pass the Alleghany Mountains and the Rocky Mountains, those in Venezuela, the Caucasus, the Dutch and British East Indies, Galicia, Mexico, the Argentine, Rumania, and Mesopotamia; small deposits of oil are also found in Germany.

The oil-zones run almost parallel to mountain ranges. There often seems to be some genetic connexion between the formation of the two, indeed it is possible that folded mountains and oil-bearing folds were produced by the same cause. The mountain folds contain oil-bearing formations chiefly only on the edges of the mountains. On the other hand there are also geologically old petroleum deposits in outcrops, salt strata, etc. of tablelands, quite unconnected with the folded mountains.

Mineral oil was not usually formed at the places where it is found to-day. Since it is a light and mobile liquid it moves under gas pressure or pressure of water accompanying it, from the lowest to the highest attainable strata. The *anticlinal theory* states that it is found in the highest elevated strata.

Mineral oil has been known for a long time. It was not, however, until the middle of the last century that its practical value was realized, and it was collected in large quantities for use in lighting and as a fuel.

FORMATION OF MINERAL OIL. There are various theories of the formation of mineral oil. One regards the oil as of inorganic origin. According to Mendelejeff's theory

¹ A. N. SACHANEN, *The Chemical Constituents of Petroleum*, New York, (1945). — V. A. KALICHEVSKY and B. A. STAGNER, *Chemical Refining of Petroleum*, New York, (1933). — E. WALDMANN, *Erdölbestandteile, bisher aus Erdöl isolierte chemische Individuen*, Vienna, (1937). — A. E. DUNSTAN, A. W. NASH, B. T. BROOKS and H. T. TIZARD, *The Science of Petroleum*, Oxford, (1938). — V. A. KALICHEVSKY, *Modern methods of Refining Lubricating Oils*, New York, (1938). — CARLETON ELLIS, *The Chemistry of Petroleum Derivatives*, New York. — A. W. NASH and D. A. HOWES, *The Principles of Motor Fuel Preparation and Applications*, 2nd ed., London, (1938).

it was formed by the action of water on metallic carbides in the interior of the earth. The work of Moissan, who obtained hydrocarbons by the action of water on various metallic carbides (uranium carbide, for example, yielded a petroleum-like mixture of hydrocarbons), and the hydrogenation of acetylene by hydrogen in the presence of nickel, to give liquids resembling petrol by Sabatier and Sendereus, and Mailhe, appear to confirm Mendelejeff's hypothesis. In spite of this it is now completely abandoned. In opposition to it is the fact that many mineral oils are optically active and contain nitrogen compounds (e.g. methyl derivatives of quinoline), as well as derivatives of chlorophyll and hæmin, hormones, etc. This can only be explained by supposing mineral oil to be of organic origin. Also, natural gas and mineral oil have never been found with hot-springs which rise from the interior of the earth.

According to modern views, mineral oil is formed partly from animal, and partly from vegetable substances, though the latter seem greatly to predominate. The plankton of sea-water may be regarded as the starting point. It settles down in the absence of oxygen and gradually decomposes. The theory of Potonié regards the bottom ooze, which in stagnant water always contains animal and vegetable remains, and especially plankton, as the most important substance from which mineral oil is produced.

In the formation of mineral oil, which takes place by decomposition processes, numerous constituents of organisms play their part, particularly proteins, carbohydrates, and fats. From protein as the starting point the nitrogen and sulphur compounds present in the oil could have been derived. Its *optical activity* is probably due to substances which have been formed from cholesterol and phytosterols, and perhaps also from resins and proteins.

C. Engler showed some time ago that products similar to petroleum could be obtained by heating animal fats under pressure. He assumed that similar processes occurred in nature, and that fats and waxes were converted into mineral oil under the influence of high temperatures and pressures. Nowadays this theory finds little support since we know that proteins and carbohydrates participate in the formation of mineral oil to a much greater extent than do the fats, which only occur in small quantities in the bottom ooze.

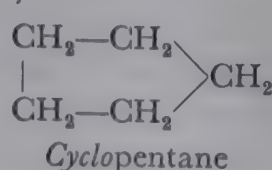
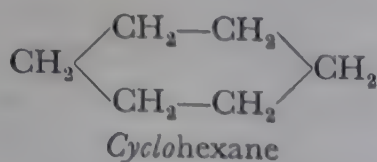
The animal-vegetable origin of mineral oil is supported by recent investigations carried out by A. Treibs. In twenty-nine kinds of mineral oil tested he found chlorophyll derivatives (e.g. deoxophylloerythroætioporphyrin) and hæmin derivatives (e.g. mesoætioporphyrin). It follows that both plants (containing chlorophyll) and animals (containing hæmoglobin) must have contributed to the formation of the oil. From the presence of porphyrins, the decomposition products of chlorophyll and hæmin, the further conclusion can be drawn that in the production of the oil an increase of temperature must have taken place, which can be estimated to be about 100–250°.

All theories which assume a process of distillation to have taken place in the production of mineral oil must be rejected since the porphyrins are not volatile. Apparently the processes which play the most important part in the formation of natural oil are diffusion, capillary action, and adsorption.

The occurrence of the œstrogenic hormones in mineral oil is interesting.

COMPOSITION OF MINERAL OIL. The composition of different oils varies to a wide extent. It is dependent on the age, manner and temperature of formation of the oil. Hydrocarbons are the chief constituents of all oils. Some kinds, such as Penn-

sylvanian oil, consist principally of *paraffin* hydrocarbons. On the other hand, Russian oils contain about 80 per cent of *naphthenes* (polymethylenes), which are cyclic hydrocarbons of the general formula C_nH_{2n} . *Cyclohexane* and *cyclopentane* belong to the series.



The Rumanian and Galician oils are intermediate in composition between the American and Russian oils.

Most kinds of mineral oil also contain larger or smaller amounts of unsaturated hydrocarbons: *olefins* C_nH_{2n} , which are made artificially by "cracking" the oil, terpenes, and *aromatic* (benzene) *hydrocarbons*. The last are contained in large amounts in some oils from the East Indies, but occur also in smaller quantities in most oils.

In addition to hydrocarbons, various compounds containing oxygen are found in mineral oil, such as naphthene carboxylic acids (*naphthenic acids*, mainly *cyclopentane* derivatives), other organic acids, phenols, *aldehydes*, and asphalt-like substances. Sulphur compounds are always present in small quantities (thiophens, thioalcohols etc.). All mineral oils contain nitrogen, the Californian oils being richest in it and containing over 2 per cent. The major part of the nitrogen is present as organic bases (Homologues of pyridine, quinoline, and *isoquinoline*).

TREATMENT OF MINERAL OIL¹. Generally speaking the crude oil is first submitted to fraction distillation, for which purpose the oil industry disposes of highly-developed continuous working plants. For the higher boiling fractions vacuum and superheated steam are used. The main fractions into which the crude oil is separated are:

Petrol, b.p. up to about 200°
Kerosene, boiling limits about 150–250°
Gas oil, boiling limits about 250–350°
Light and heavy lubricating oil fractions
Residue.

Petrol is used in enormous quantities as a motor fuel, chiefly for motor-cars and aeroplanes. Only relatively small quantities are further separated into narrower fractions for special purposes, e.g. for use as solvents, extracting agents, and for chemical cleaning. The demand for petrol has become so great that it can no longer be satisfied by the direct distillation of crude oil. In the last two decades ever-increasing amounts of petrol have, therefore, been produced by thermal decomposition of the higher boiling fractions of mineral oil (cracking process). This cracking is carried out in various ways and mostly under moderate pressure at temperatures of about 470–500°. The process and the following separation of the petrol fraction are carried out in continuous working plants. To-day already, more than half the world production of petrol is obtained by this means. The raw materials used in the cracking process are distillation residues, usually crude oils from which only the lightest fractions have been removed.

¹ E. H. LESLIE, *Motor Fuels. Their Production and Technology*, London, (1923). — J. E. LATTA and H. L. KAUFFMAN, *Petroleum Distillation and Testing*, New York, (1939).

Another circumstance has greatly contributed towards the rapid introduction of the cracking process. One of the most important properties of a motor fuel is its resistance to knocking, for this largely determines the amount of energy that can be obtained from it in an internal combustion engine. By the resistance to knocking of a fuel is understood the degree of compression, to which the mixture of petrol and air may be subjected in the motor before ignition, without any irregularities occurring in the combustion process that would cause the so-called knocking of the motor. It has been found that the resistance to knocking of a fuel is in the first place dependent on its chemical composition. It is smallest for the normal hydrocarbons of the methane series, greater for the olefins and hydroaromatic, and greatest for the aromatic and highly-branched paraffin hydrocarbons. Furthermore, it generally decreases with increasing molecular weight. As a practical measure of the resistance to knocking of a petrol the so-called octane number is nowadays universally used. It indicates the percentage of *isooctane* (2:2:4-trimethyl-pentane) in that mixture of *isooctane* and *n*-heptane which has the same knocking characteristics as the petrol under examination. Thus the very knock-resistant *isooctane* has the octane number 100, while *n*-heptane, which readily causes knocking, has the octane number 0. Cracked petrols have, owing to their content of unsaturated hydrocarbons, considerably higher octane numbers and therefore a greater commercial value than the saturated products obtained by direct distillation from crude oil. For this reason, petrols of the latter type are often nowadays subjected to a special cracking process, merely to improve their knocking properties ("reforming process").

It may be mentioned here that considerable quantities of petrol fractions with low boiling points are moreover obtained from natural gases occurring in the mineral oil districts.

The purified fraction of crude oil distilling after petrol is *kerosene* having a boiling range of about 150–250° and which was originally the main product of the mineral oil industry. Its importance has greatly decreased. The next higher fraction however, the *gas oil* (boiling limits about 250–350°) enjoys a rapidly increasing importance. The name originates from its former use, namely the production of oil gas, which served to illuminate railway carriages. Nowadays, gas oil is used in ever growing quantities as a fuel for central heating and particularly for Diesel engines.

The fractions of mineral oil with higher boiling points are worked up into *lubricating oils* of various kinds, whenever their chemical composition allows it. These mineral lubricating oils have the advantage of possessing a greater chemical and thermal resistance than the fatty oils of vegetable and animal origin which were formerly exclusively used. Most of the paraffin wax present in crude oil is found in these lubricating oil fractions. The latter are, therefore, often in the form of a semi-solid mass, especially when the starting material is rich in it. In the production of lubricating oils this solid paraffin must, of course, be removed, since it would raise the solidification temperature of the oil. This is accomplished by filtration at low temperatures with the aid of solvents or solvent mixtures. The paraffin cake which thus remains on the filters is the raw material for the production of paraffin wax; however, owing to the large quantities obtained, only part of it can be used for this purpose.

Finally, the *distillation residues* form one of the most important products of the

mineral oil industry. After being duly diluted they are used as fuel oils in ships. The residues from cracking are particularly suitable, whilst those from the direct distillation of crude oil furthermore find manifold uses in the paint trades, and as petroleum asphalt or petroleum pitch in road construction.

As regards the *refining* of the various petroleum products the following may be noted: petrol, if obtained other than by cracking, does not generally require extensive refining; if necessary, a small quantity of strong sulphuric acid will answer the purpose. The refining of petrol, obtained by cracking, is nowadays often carried out with less concentrated sulphuric acid, in order to protect the desirable aromatic and olefinic constituents. Recently other refining agents more suitable for this purpose have been introduced, which furthermore make it possible to refine the petrol continuously in the vapour phase. The two most important of these refining agents are concentrated phosphoric acid, which is generally used on a carrier, and zinc chloride, which is used in a concentrated aqueous solution.

When refining kerosene the main problem consists in bringing the percentage of aromatic hydrocarbons down to the point at which the flame is no longer sooty. For this selective removal of the aromatic hydrocarbons, extraction with liquid sulphur dioxide has been successfully used for a long time (Edeleanu).¹ Similar physical refining methods using selective solvents have recently been introduced for the refining of lubricating oils as well.

The treatment and fractionation of mineral oil is determined essentially by its composition. Whilst the North American oils give 10–20 per cent benzene, the Caucasian oils give only up to 5 per cent. The latter are therefore rich in lubricating oils (60–65 per cent).

From the non-volatile residues after distilling American oils at 300°, the valuable vaseline is obtained. It has found extensive use in making pomades and salves and as a lubricant.

An important by-product of the petroleum industry is *paraffin wax*. It is obtained from the lubricating oil fraction by crystallization. Paraffin wax consists of a mixture of solid hydrocarbons. Its melting point varies with its composition, but usually lies between 51° and 55°. Other products with a higher melting point (60°, hard paraffin) and a lower melting point (45°–50°, soft paraffin) are commercial products. The principal use of paraffin wax is in the manufacture of candles, but it is also used for impregnating match-sticks, finishing fabrics, as an insulator, etc. Paraffin wax of good quality and in good yield, can also be obtained by distillation of various other substances, such as lignite, bituminous shale, and peat. Large quantities are produced, particularly in the *low-temperature carbonization* of lignite, a dry distillation process at a dull-red heat. In addition, a liquid fraction, "*solar oil*", used as a fuel for motors, is produced.

Formerly, paraffin wax was obtained by distillation of *ozokerite*, or *mineral wax*, a mixture of solid hydrocarbons of the paraffin series, mentioned above. In more recent times this method has fallen into disuse. Mineral wax is first purified with sulphuric acid and treated with a decolorizing agent, when the useful substance *ceresin* is produced. It is used in the manufacture of glazed paper, oil-cloth,

¹ J. C. L. DEFIZE, *On the Edeleanu Process for the Selective Extraction of Mineral Oils*, London, (1938). — A. ABRAHAM, *Asphalt and Allied Substances; their Occurrence, Modes of Production, Uses in the Arts and Methods of Testing*, 4th ed., London, (1938).

and candles, in the preparation of leather polishes, and as a substitute for Carnauba wax and bees-wax.

The so-called *petroleum pitches*, which form the residue from the distillation of the oil are obtained particularly in America from oils rich in asphalt, and are of great importance in road construction as well as in the manufacture of electrode-carbon for the production of aluminium. *Natural asphalt* is related to petroleum pitch or petroleum asphalt. Natural asphalt occurs in considerable quantities in the Asphalt Lake of Trinidad, and also in many other places (Venezuela, Mexico, California, the Dead Sea, Val de Travers in the Neuchâtel Canton, French Rhône valley), and is largely used. The pitch obtained in the distillation of lignite has similar properties and serves for the same purposes as the types of asphalt mentioned above. The same is true of the pitch obtained as the residue from the distillation of coal-tar. The latter is, however, quite distinct in its chemical composition from natural asphalt, consisting for the most part of benzene derivatives.

METHODS FOR THE ARTIFICIAL PRODUCTION OF PETROL. Owing to the extraordinary development of the motor-car and aeroplane in the last decades, and the use of oil fuel in ships, the supply of and the demand for mineral oil products have increased considerably within recent years. Whilst the world production of mineral oil in 1900 was ca. 20 million tons, it increased to 50 million tons in 1913, and to ca. 287 million tons in 1942.

This considerably increased demand for petrol in particular has stimulated the development of the technical production of petrol. The most important of these processes use as raw materials the olefins formed as by-products in cracking operations. The importance of these processes lies not only in the quantity of products thus obtained, but also in their excellent quality as regards resistance to knocking. When it is realized that in the U.S.A. ca. 14 million tons of these cracking gases are available annually, the importance of this source of petrol is obvious. The principal olefins in these cracking gases are ethylene, propylene, and the butylenes.

The most important process for the production of petrol from cracking gases is based on the polymerization of the olefins present, either by the application of high temperatures and pressures alone or with the aid of catalysts. The most common catalyst is phosphoric acid on a suitable carrier, such as silicic acid. These polymerization petrols have excellent knocking characteristics.

The methods for obtaining *isooctane* from the *isobutylene* or *isobutane* in cracking gases have already been described in the section on octanes.

In contrast to the enormous stocks of coal of the world the mineral oil reserves are rather limited, so that, in consequence of the greatly increased exploitation of the latter, a shortage of this natural product may be foreseen at a time not very far distant. Attempts have therefore been made to devise methods of transforming coal into mixtures of hydrocarbons similar to petrol, which could replace the natural products.

At present there are two methods in use for the artificial production of petrol. They both use as starting materials carbonaceous substances to which hydrogen is added in the presence of catalysts:

1. Directly, by the action of hydrogen on coal at pressures of about 200 to 700 atmospheres and temperatures of about 400–500°.
2. Indirectly, by conversion of coal to water gas and reaction of the mixture

of carbon monoxide and hydrogen thus obtained at ordinary or slightly increased pressures and at a temperature of about 200°.

The first method is that of the I.G. process of catalytic pressure hydrogenation. Even before the first World War, Bergius had shown that it is possible to convert coal into oils by the addition of hydrogen at high pressures. Using their experience with catalysts and high-pressure technique acquired in the syntheses of ammonia and methanol, the I.G. Farbenindustrie has since 1925 developed this process, for the technical realization of which, the discovery of catalysts immune to poisons (e.g. molybdenum compounds) was decisive.

As starting materials not only anthracite and lignite can be used, but also low-temperature carbonization tar from lignite, and shale oils. The products obtained consist of a mixture of paraffins, naphthenes, and aromatic hydrocarbons. This process is also important for the mineral oil industry as it makes it possible to obtain a greater proportion of oils with lower boiling points, especially petrol, from crude oils.

The second method for the artificial production of mineral oil products is that of the Fischer-Tropsch-Ruhrchemie process. Exactly as in the synthesis of methanol (see p. 88) water gas is first produced, i.e. the raw material is broken down into carbon monoxide and hydrogen. All kinds of coal and coke can be used as raw materials, as the processes for the production of water gas can to a great extent be adapted to the type of fuel available.

From the water gas liquid hydrocarbons are then built up, using catalysts at ca. 200° and normal or slightly increased pressures. Iron, nickel, and cobalt can be used as the catalysts. The hydrocarbons obtained consists almost exclusively of *n*-paraffins, and olefins if any. Petrol, good Diesel oil, and paraffin wax are thus produced.

Petrol can, moreover, be produced by the *low-temperature carbonization* of anthracite and lignite. Petrol and tar are actually mere by-products here, the main product being the low-temperature coke. Coal when distilled at 450-600° produces the so-called *low-temperature tar*. Compared with high-temperature tar, the low-temperature tar of anthracite contains a smaller percentage of aromatic hydrocarbons. This fact has already been known for some time (Williams 1857, Schorlemmer 1863-66). Low-temperature tar from lignite is rich in paraffin hydrocarbons, and lubricating oils and paraffin wax may be obtained from this type of tar as well. Fairly large quantities of oil containing phenols are also present in low-temperature tars from anthracite and lignite. It is only in recent times, however, that low-temperature carbonization has been extensively investigated (A. Pictet, Fr. Fischer, etc.) and carried out on a technical scale.

Unsaturated aliphatic hydrocarbons

By the term "*unsaturated*" hydrocarbons is understood those hydrocarbons which are poorer in hydrogen than the paraffins. They belong to different homologous series, the proportion of carbon to hydrogen being different from that in the paraffins. Their compositions are represented by the following general formulæ:



Hydrocarbons with an odd number of hydrogen atoms are not found amongst aliphatic compounds. A few cases of such compounds are known in the aromatic (benzene) series, but they are very unstable. They will be considered later.

Olefins or hydrocarbons of the ethylene series

THE ETHYLENIC HYDROCARBONS have the general formula C_nH_{2n} , which is also shared by a second series of hydrocarbons, the *polymethylenes*, or *naphthenes*. Although there are many points of relationship between the olefins and naphthenes, there are also many, and considerable differences. The olefins have, in general, a stronger unsaturated character, and enter more easily into addition reactions than do the polymethylenes. There is also a structural difference, the polymethylenes being cyclic compounds, and the olefins having an open chain.

All ethylenic hydrocarbons possess the same percentage composition, as is seen from their formulæ. They contain 85.7 per cent. of carbon and 14.3 per cent of hydrogen. Analysis alone is therefore insufficient to enable a distinction to be made between two or more olefins. A determination of molecular weight is required which can be carried out by the usual physical or physico-chemical methods (determination of vapour density, cryoscopic or ebullioscopic methods). There is also another method of determining the molecular weight of an olefin. Addition products are made from the compound, e.g. addition compounds with bromine, which show sufficiently great differences in composition to throw light on the nature of the original hydrocarbon.

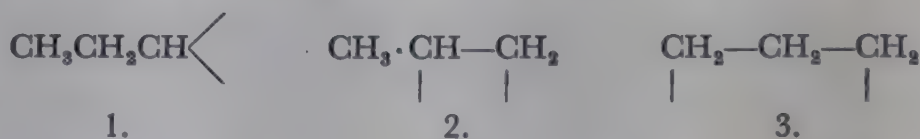
Thus, the addition product of ethylene, C_2H_4 , and bromine, $C_2H_4Br_2$, contains 12.76 per cent C, 2.14 per cent H, and 85.10 per cent Br, whilst the addition product of the next higher homologue, propylene, C_3H_6 , with bromine, $C_3H_6Br_2$, contains 17.82 per cent C, 2.99 per cent H, and 79.20 per cent Br.

Structure and spatial configuration of the olefins. Ethylenic hydrocarbons differ from the paraffins in containing two atoms of hydrogen less, and they can easily be converted into the saturated hydrocarbons by hydrogenation. The question now arises at which carbon atoms the two hydrogen atoms are missing, and what happens to the two carbon valencies not saturated by hydrogen.

With regard to the position of the two carbon valencies not saturated by hydrogen there are three possibilities to be considered:

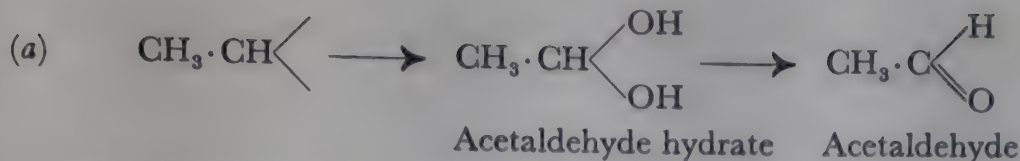
1. They are both attached to the same carbon atom.
2. They are attached to adjacent carbon atoms.
3. They are attached to non-adjacent carbon atoms.

These three cases are illustrated by the following formulæ:

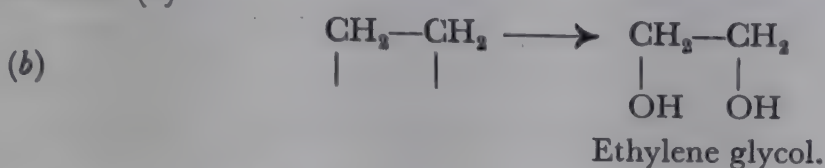


It is easily shown that in the case of the olefins the second possibility is the only one that can be correct. This is indicated by the following considerations:

(a) To *ethylene*, C_2H_4 , the first member of the series, two OH groups may be added by treatment with potassium permanganate (G. Wagner). They doubtless saturate the carbon valencies which are not saturated by hydrogen. If these lie on the same carbon atom, and ethylene has the formula (∇), the oxidation product must be acetaldehyde hydrate, which, being very unstable would give acetaldehyde:



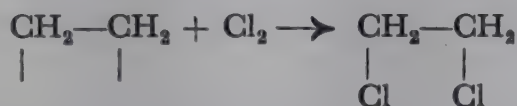
Actually, however, the product of the action of potassium permanganate on ethylene is a compound which is quite different from acetaldehyde, and which, on account of its further oxidation to a di-aldehyde, and ultimately to a dicarboxylic acid, must be a dihydric primary alcohol (ethylene glycol). In ethylene, therefore, one hydrogen atom must be missing at each carbon atom, agreeing with formula (b).



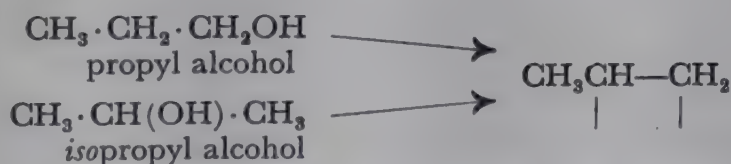
Investigation of the halogen addition compounds of ethylene leads to the same result. If formula (a) is correct the compounds of ethylene with two atoms of chlorine or bromine must be identical with those substances obtained by the action of phosphorus pentachloride and pentabromide on acetaldehyde:



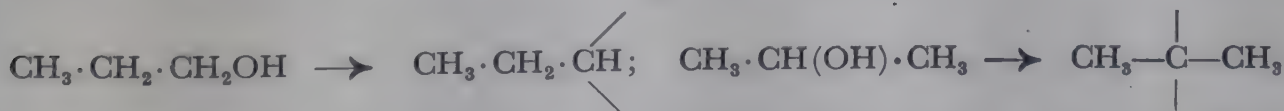
Experiment shows, however, that this is not the case. The addition product of chlorine and ethylene and the product obtained by the action of phosphorus pentachloride on acetaldehyde are different. Ethylene has therefore reacted in the following way:



(b) The second member of the olefin series is *propylene*, C_3H_6 . It can be obtained from two different hydroxy-derivatives of propane — propyl alcohol, and *isopropyl* alcohol — by splitting off water:



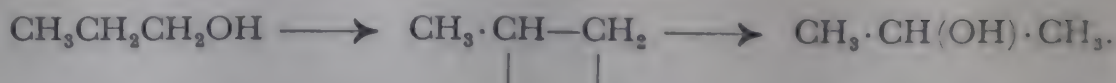
The fact that two different propyl alcohols give *the same* propylene points to the conclusion that the two carbon valencies no longer saturated with hydrogen are attached in the latter to adjacent carbon atoms. If hydroxyl and hydrogen were split off from the same carbon atom, propyl and *isopropyl* alcohol would yield two different unsaturated hydrocarbons:



Similarly the unsaturated carbon valencies cannot be on the first and third carbon atoms of propylene, since then the removal of water from *isopropyl* alcohol would not lead to this hydrocarbon.

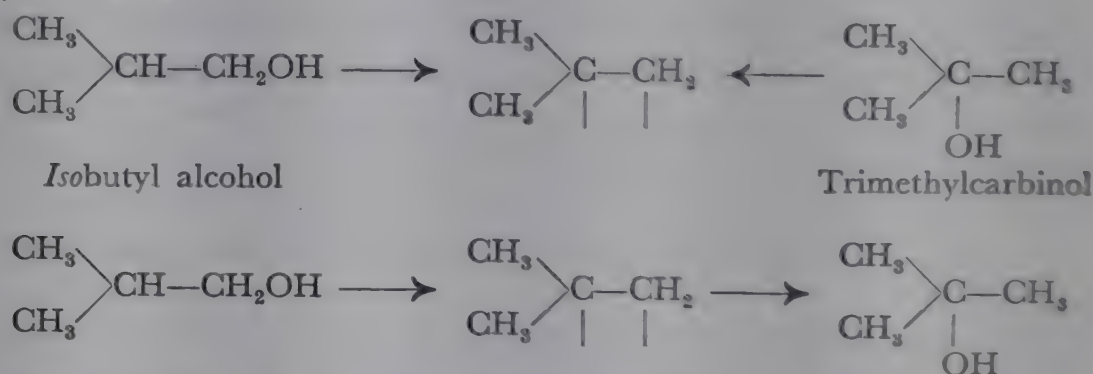
A further confirmation is provided by the fact that it is possible to obtain

propylene from propyl alcohol by removal of water, and to make isopropyl alcohol by the addition of water to propylene:



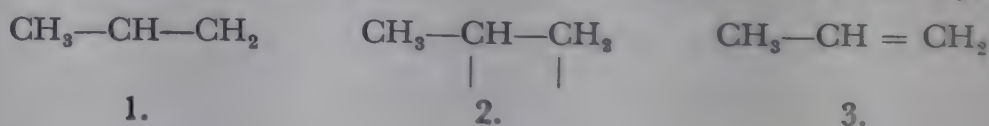
It is obvious that this excludes both the formula $\text{CH}_3\text{CH}_2\text{CH} \begin{smallmatrix} \diagup \\ \diagdown \end{smallmatrix}$ and $\text{CH}_2 - \text{CH}_2 - \text{CH}_2$ for propylene.

(c) As a third example, the reactions of a somewhat higher olefin, isobutylene, C_4H_8 , will be considered. This hydrocarbon can be obtained from both isobutyl alcohol and trimethylcarbinol (of which the formulæ are known by synthesis) by removal of water (Butlerov). The isobutylene obtained from isobutyl alcohol, on treatment with dilute sulphuric acid, adds on water and affords trimethylcarbinol.



The splitting off and addition of water therefore takes place by the removal or addition of the elements of water at two adjacent carbon atoms, and hence the two carbon valencies not saturated by hydrogen in isobutylene must be attached to neighbouring carbon atoms.

These considerations show without doubt that the olefins differ from the paraffin hydrocarbons by having two hydrogen atoms less, these two hydrogen atoms being removed from adjacent carbon atoms. The question now arises, what happens to the two free carbon valencies. There are two possibilities. These two adjacent carbon atoms could remain in an unsaturated state, as shown by the formulæ 1 and 2, or the two unsaturated carbon valencies could mutually saturate each other, when formula 3 is obtained for the hydrocarbon:



The last formula contains a so-called "carbon double bond" or *ethylenic linkage*. This formulation of the olefins and their derivatives is preferred to the other two. This method of writing the formula has come into general use, and is employed in this book. We shall see, however, that it does not explain sufficiently all the properties of the olefins.

The most important reasons for adopting the double bond rather than a formulation with unsaturated carbon atoms are the following: If unsaturated (trivalent) carbon atoms could exist, it would be expected that they would occur singly, or in odd numbers in aliphatic hydrocarbons, and that unsaturated hydrocarbons of the formulæ $\text{C}_n\text{H}_{2n+1}$, $\text{C}_n\text{H}_{2n-1}$, $\text{C}_n\text{H}_{2n-3}$, etc., would be stable. As already stated, this is not the case; unpaired "unsaturated" carbon atoms do not

exist. If it were assumed that "trivalent" carbon atoms could exist it would not be easy to see why they should always occur next to each other, and not more widely separated in the carbon chain.

The double carbon linkage between carbon atoms does not, however, explain sufficiently one very important property of olefins. From the examples mentioned above, and many others which will be considered later, it is seen that ethylenic substances always tend to react by addition, and that the added atoms or groups attach themselves to the two carbon atoms which are "doubly" linked. Hence, there can be no doubt that these represent the unsaturated points of the molecule. The formulation with the double bond does not account for this behaviour, which would be much better explained by using unsaturated carbon atoms. Since, however, as has been shown above, there are many difficulties in the way of accepting the latter, it is necessary to ask whether it is not possible to steer a middle course between the two formulæ so as to express the nature of the olefins more correctly.

If the two carbon atoms of ethylene require more than the normal amount of affinity of a single bond for their mutual saturation, but do not use up completely the amount associated with the two links, they may, in a certain sense, be said to be linked by a "double" bond, and yet at the same time they may possess an amount of unsaturated residual affinity, which enables the molecule to add on other atoms. This view, due to Thiele, can be illustrated by the following formula:



The dotted lines represent partial valencies.

A distribution of valency in this way explains not only the unsaturated nature of the carbon atoms, but also makes it clear why in olefins an unsaturated trivalent carbon atom is not stable alone, or at two places in the carbon chain separated by some distance. The existence of *neighbouring* unsaturated carbon atoms is only made possible as it is not a whole valency unit, but only part of one which comes into force externally, and the remaining part can be used in linking the adjacent carbon atom by a "double" bond. Thiele's formula, which explains in a simple manner many of the properties of the olefins, without, however, solving completely the problem of the ethylenic linkage, has gained much support. If, nevertheless, the ethylenic hydrocarbons are formulated in this book with the double bond in general use at present, this must not be thought to imply a rejection of Thiele's conception, but is merely a simple method of writing. *The student should always associate with the idea of the double bond, the existence of unsaturation of the carbon atoms even if this is not directly shown in the formula.*

For the electronic concept and interpretation of the carbon double linkage see p. 62.

The hypothesis of the ethylenic double bond leads to conclusions of which the accuracy can be tested, in part at any rate, by experiment. The results of these experiments provide a valuable means of judging the truth of the hypothesis.

It is assumed, on the basis of experiment, that in the *single* carbon linkage, the direction in which the two carbon valencies which form the link act is a straight line, and that free rotation of both carbon atoms with their attached atoms or groups is possible about this line. Of course, this does not mean that the rotation is going on continually; it appears probable, on the contrary, that the

two carbon atoms are fixed in a certain spatial position with respect to each other, the other groups attached to the carbon atoms acting as directive forces and determining the stable position of the system.

If, on the other hand, two carbon atoms are linked by *two* valency bonds, as the hypothesis of the double bond assumes, their free rotation with respect to each other must be restricted, since the rotation would cause a rupture of the double bond, and the separation of the carbon atoms. Owing to the presence of a double bond the molecule must have one definite spatial configuration, which is shown in fig. 7 (the four valencies of the carbon atom are directed to the corners of a tetrahedron):



Fig. 7

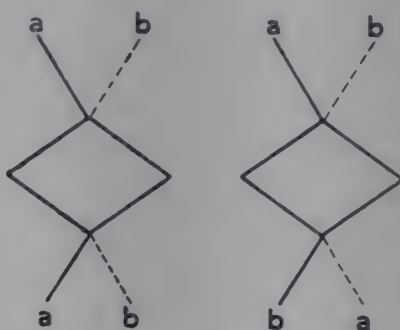


Fig. 8

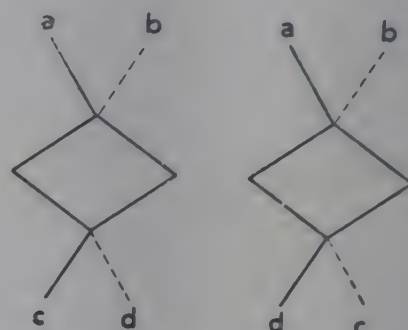


Fig. 9

As a result of this stable spatial configuration of the molecule it follows that ethylenic compounds of the general formulæ



must be capable of existing in two stereoisomeric forms (figs. 8 and 9), whilst olefin derivatives of the type $aaC=Caa$ and $abC=Caa$ do not show this isomerism. Actually this theoretical conclusion, first thoroughly investigated by J. Wislicenus (1887) can be verified by experiment, and not a single observation has been made which does not agree with it. The existence of the isomeric ethylenic compounds is, therefore, an important confirmation of the existence of the "double bond" in olefins.

If the space diagrams (Figs. 7–9) are projected on to the plane of the paper, the usual projection formulæ of ethylenic substances are obtained. These will be used in future throughout the book.

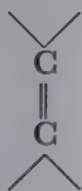


Fig. 7a.

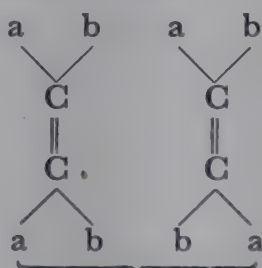


Fig. 8a.

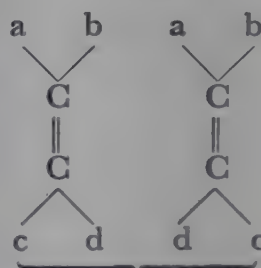


Fig. 9a.

The formulæ make it clear that the isomerism of the ethylene derivatives, which is also called *geometric isomerism*, is a type of *cis-trans isomerism*, where in one form the same "substituents" are on the same side of this double bond (a, a in Fig. 8), and in the isomeric form, on opposite sides. The isomerides cannot be superimposed by any rotation of the molecule, and are not mirror images (see p. 100). Such compounds are called *diastereoisomerides*, and the phenomenon

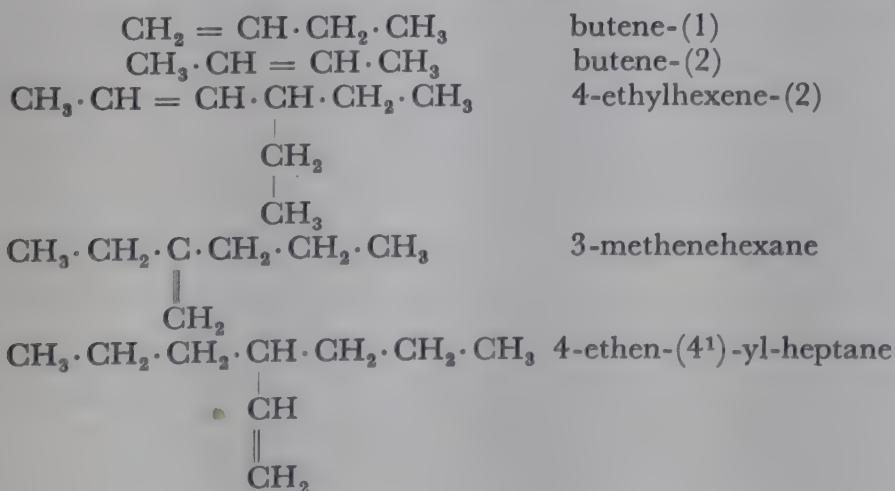
diastereoisomerism. All diastereoisomerides, including the spatial isomeric olefins and their derivatives, have different physical and chemical properties. The fundamental reason for this is that the distances between corresponding atoms (e.g. a,a in the isomerides in Fig. 8) in the two isomerides are different. This makes the affinity and stability relationships different in the two forms, and this is reflected in different physical and chemical properties.

Recently it has been found possible to measure, by the use of physical methods, the actual differences in the distances between corresponding atoms in *cis-trans* isomerides. Thus, Debye determined the distance between the two chlorine atoms in *cis*-dichloroethylene to be 3.6 Å, and in the *trans*-compound, 4.1 Å, by an interferometric method (investigation of X-rays scattered at individual molecules).

When the double bond of diastereoisomeric ethylenic compounds is removed by addition of certain other atoms or groups, the isomerism disappears. This proves that the isomerism is actually due to the double bond, and the special configuration of the molecule produced by it. As soon as the double bond is removed by the addition, the possibility of free rotation is restored owing to the presence of the single carbon bond, and the compounds produced from the two diastereoisomeric ethylenic compounds arrange themselves in the most stable spatial configuration.

Nomenclature of the olefins. For naming the ethylenic hydrocarbons, the ending originally chosen was “ylene”, which was added to the name of the alkyl radical concerned. This nomenclature is still in common use to-day, particularly for the lower members. Thus, the first olefins are called *ethylene*, C_2H_4 , *propylene*, C_3H_6 , *butylene*, C_4H_8 , *amylene*, C_5H_{10} , *hexylene*, C_6H_{12} , and in general, *alkylenes*. The radical CH_2 , free methylene, is exceedingly unstable; its half-life period is only a few thousandths of a second.

The Geneva nomenclature prescribes the ending -ene for characterizing the ethylenic hydrocarbons, e.g. ethene, pentene, octene, etc., or, in general, alkenes. The position of the double bond is indicated by a number placed in parentheses behind the name. It gives the number of the carbon atom at which the double bond starts. The same general principles hold as for the naming of the paraffins. If it is possible to choose the name so that the double bond lies in one of the longest carbon chains in the molecule this is done, and the enumeration begins at the end of the principal chain nearest to the double bond. In other cases, a side chain linked to a principal chain by a double bond is characterized by the ending -ene, and a side-chain containing a double bond in another place by the ending -enyl.

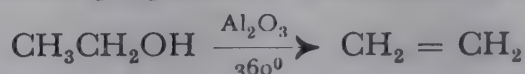


The name *olefin*, or oil-producer, is given to the alkylenes because they easily combine with chlorine and bromine forming oily liquids, immiscible with water, a property which was recognized a long while ago, and which led to the name olefiant gas being given to ethylene.

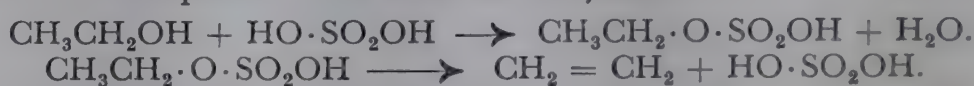
Occurrence and preparation of the olefins. Olefins are found in many mineral oils, but usually in small amounts. Some Canadian oils are said to be richer in them. The compounds C_6H_{12} to $C_{13}H_{26}$, amongst others, have been isolated from oils in a pure state. They occur in considerable amounts in the petrol and kerosene fractions produced by the artificial cracking of lubricating oils. Their formation has also been observed in the pyrogenic decomposition of other organic substances. The presence of olefins in coal-gas and tar is due to this. Finally the action of acids or water on metal carbides gives rise to small amounts of olefins.

The following are *methods of preparation* of the alkylenes:

1. The removal of water from saturated aliphatic alcohols. This removal of water can be effected by passing the vapour of the alcohol over heated contact catalysts (Ipatiev). Good catalysts for the purpose are alumina, aluminium silicate, graphite, aluminium phosphate (Senderens), and sand. The process is used at present, e.g. for the technical preparation of ethylene from ethyl alcohol:



Another method of dehydrating alcohols is to warm them with sulphuric acid, either concentrated or slightly diluted, or with zinc chloride. When sulphuric acid is used an acid ester of the acid is formed as an intermediate compound, and breaks down into sulphuric acid and the alkylene:



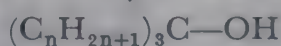
This reaction, which is an important method of preparation for the first members of the olefin series is often accompanied by side reactions when the higher alcohols are used, which detracts from its value. Thus, sometimes mixtures of isomeric alkylenes are obtained, their production being due to the splitting off of water from different sides of the chain, or to the partial displacement of the double bond in the olefin under the influence of the sulphuric acid.

Zinc chloride acts by first combining with the alcohol forming a hydroxo-acid ester (I) which then breaks down into the hydroxo-acid of zinc chloride (II) and the olefin:



From the long list of other dehydrating agents which can be used for dehydrating alcohols, but which may be more or less effective for any particular alcohol, may be mentioned: phosphorus pentoxide, potassium bisulphate, oxalic acid, formic acid, and phthalic anhydride.

Of all alcohols, the tertiary alcohols (i.e. those in which the OH group replaces a hydrogen atom attached to a tertiary carbon atom) lose water the easiest.



Olefins are formed from them even by very mild treatment, very often by the action of glacial acetic acid, hydrogen halides, or acid chlorides.

For the preparation of the higher alkylenes the distillation of certain esters

of the alcohols is often used. The palmitic acid ester of dodecyl alcohol gives, on distillation, palmitic acid, and the olefin dodecylene (Krafft):



Tschugaeff has found the action of heat on S-methyl xanthates, $\text{RO} \cdot \text{CS} \cdot \text{SCH}_3$, suitable for the preparation of unsaturated compounds.

2. A second method for obtaining alkylenes is the removal of hydrogen halide from *alkyl halides*:



The removal of hydrogen halide is usually carried out by ethyl alcoholic, or better methyl alcoholic potash. Ethers are often formed as by-products according to the following equation:



Alkyl halides can be decomposed into olefins and halogen hydrides by passing them over heated alumina, red-hot quicklime, or heated barium oxide. The halogen hydride is most easily removed in the case of tertiary alkyl halides.

3. The withdrawal of halogen from dihalogen compounds of the paraffins which have the two halogen atoms attached to adjacent carbon atoms also gives rise to alkylenes:



Metals such as zinc, or the zinc-copper couple are suitable for the removal of bromine.

4. Certain olefins may be prepared by the action of alkylmagnesium salts on alkylene bromides in which the double bond is in the α, β -position with respect to the halogenated C-atom:



(Tiffeneau, Barbier, Grignard, Kirmann).

5. Of greater importance, particularly as regards the elucidation of constitutional questions, is a method of obtaining olefinic hydrocarbons by the dry distillation of quaternary ammonium bases. This process, which goes under the name of "*exhaustive methylation of amines*" will be dealt with later in connection with the aliphatic amines. The course of the reaction can be represented by the following scheme:



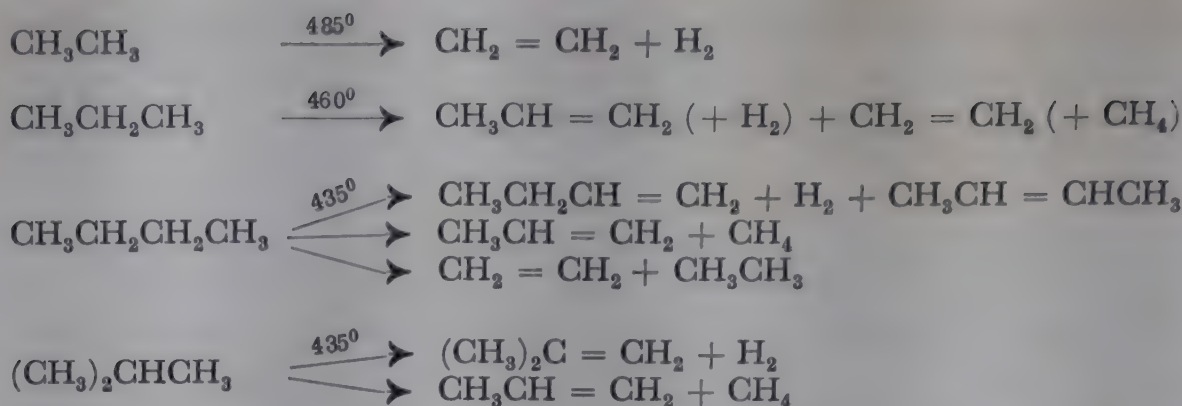
When nitrous acid acts upon primary amines, primary alcohols are chiefly obtained (see later), but considerable quantities of alkylenes are often obtained as by-products:



6. The lower unsaturated hydrocarbons (ethylene, propylene, butylene etc.), which have become important for a great variety of syntheses, are nowadays prepared by the cracking process from the saturated petroleum hydrocarbons. The cracking is carried out in the vapour phase under atmospheric pressure and at high temperatures (up to 700°C) or in the liquid or mixed phases under high pressures. There are also catalytic procedures in use in which AlCl_3 or other catalysts are utilized to facilitate the splitting processes.

By these cracking processes low-molecular olefins are obtained from the lower paraffin hydrocarbons, e.g. ethylene from ethane, propylene and ethylene from propane, and butylenes and isobutylene from butane and isobutane respectively:





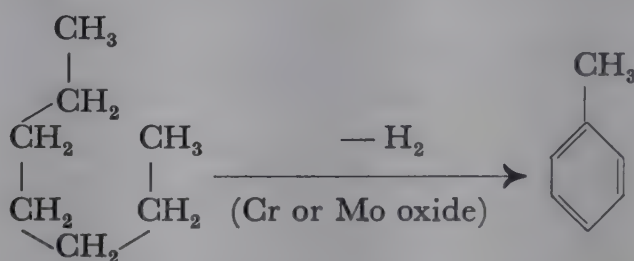
From these olefins which are in this way accessible in huge quantities, the American industry now prepares a large number of technically important products, as for instance, anti-knock, *isooctane*-rich motor fuels, aromatic compounds (toluene, benzene, naphthalene), butadiene as a starting material for synthetic rubber, etc. Mineral oil has thus become, as has been coal-tar in former times, the starting point for large organic chemical industries. Some examples of such modern syntheses follow:

a) Polymerization of *isobutene* to *isooctenes* by H_2SO_4 or H_3PO_4 , followed by hydrogenation to give (anti-knock) *isooctane* (see page 36).

b) Dehydrogenation of butene to butadiene by the action of special catalysts (Cr, Mo, V, or Zn oxides deposited on Al_2O_3 or SiO_2)



c) Catalytic dehydrogenation of *n*-heptane to form toluene, in the presence of suitable metal oxides:



Physical properties of the olefins. The first three members of the olefin series are gases, then follow liquids which are immiscible with water. The highest members are solid.

		b.p.			b.p.
Ethylene	C_2H_4	—103°	Heptylene-(1)	C_7H_{14}	94.5°
Propylene-(1)	C_3H_6	— 48°	Octylene-(1)	C_8H_{16}	120.5°
<i>n</i> -Butylene-(1)	C_4H_8	— 6.7°	Nonylene-(1)	C_9H_{18}	150°
<i>n</i> -Amylene-(1)	C_5H_{10}	+ 30.2°	Hexadecylene-(1)	$\text{C}_{16}\text{H}_{32}$	155°*
Hexylene-(1)	C_6H_{12}	+ 63.9°	Octadecylene-(1)	$\text{C}_{18}\text{H}_{36}$	179°*

*under 15 mm pressure.

The alkylenes burn with sooty flames. The *molecular refraction* is an important constant in connection with the olefins. Whilst the molecular refractions of the paraffins are usually accurately given by the sum of the atomic refractions, the value obtained in this way for the olefins and their substitution products is less than that determined experimentally. This difference, which is due to the presence of the double bond, is referred to as the *increment* due to the double bond. It is designated by the sign \overline{F} . It varies only a little about a mean value which amounts to about 1.73–1.9 for a single ethylenic linkage, and double this for two linkages (Brühl, Auwers, Eisenlohr).

		Calc. from atomic refractions	Found	F
Mol.refraction for amylene	C ₅ H ₁₀	23.09	24.83	1.74
„ „ hexylene	C ₆ H ₁₂	27.70	29.65	1.95
„ „ octylene	C ₈ H ₁₆	36.94	38.75	1.81

The atomic refraction of carbon is therefore not constant, but varies with its degree of saturation. It is higher for doubly linked carbon atoms than for those which are singly linked. In addition, as was shown by Eijkman, the position of the ethylenic linkage within the molecule exerts an effect on the amount of the increment, so that determinations of refractivity have some importance in the derivation of constitutional formulæ (see also the work on the "parachor", p. 122).

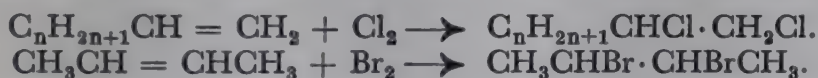
Chemical properties of the olefins. The unsaturated nature of the olefins is the cause of their great chemical reactivity. This is shown in their great tendency to enter into addition and polymerization reactions. The addition of the incoming atoms and molecules mostly takes place to the two unsaturated carbon atoms which are at the ends of the double bond. The following examples illustrate this:

1. The alkylenes can easily add on hydrogen in the presence of catalysts, such as platinum black (Fokin, Willstätter) or finely divided nickel (Sabatier). They are thus converted into paraffins.¹



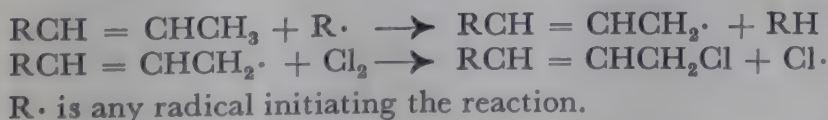
This reaction usually takes place at a temperature of about 100°.

2. Chlorine and bromine add on very readily to ethylenic hydrocarbons.



These reactions take place usually so readily and so completely, that they can be used for the separation of olefins from mixtures of hydrocarbons, and (especially the addition of bromine) for the determination of the ethylenic linkage volumetrically. The titration is carried out until the bromine solution is no longer decolorized. Suitable solvents are chloroform, carbon tetrachloride, carbon disulphide, glacial acetic acid, and ether.

A hydrogen of the methyl group in unsaturated compounds of the general formula $\text{R} \cdot \text{CH} = \text{CHCH}_3$, however, may also be *substituted* at higher temperatures by chlorine, bromine, or by bromine using bromosuccinimide, without addition of halogen to the double bond. This reaction, which has lately increased in importance, takes place through radicals and may be represented by the following formulation:



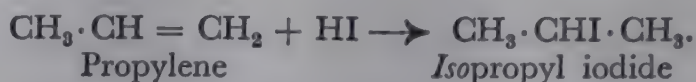
3. The halogen hydrides also add on readily to ethylenic hydrocarbons.

¹ See the monograph on hydrogenation: CARLETON ELLIS, *Hydrogenation of Organic Substances*, 3rd. ed., New York, (1930).

Hydrogen iodide adds on the most easily, then hydrogen bromide. Hydrogen chloride does not add on so readily, and often requires a higher temperature:



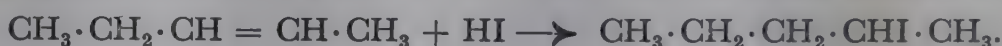
If the two carbon atoms at the ends of the double bond are not attached to the same number of hydrogen atoms, the halogen atom of the halogen hydride adds on preferentially to the carbon atom with the least hydrogen. This is known as Markovnikov's rule. The isomeric addition product is usually only produced in very small amount.



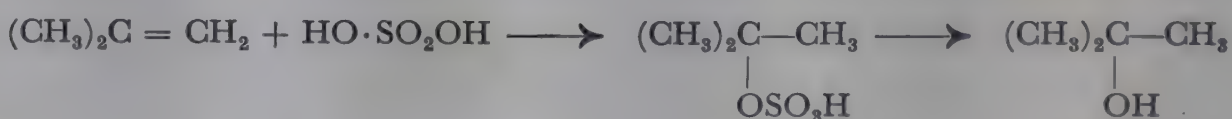
Occasionally the solvent used in the reaction may alter the proportions of the two isomerides formed. If, for example, hydrogen bromide gas is added to pentene-1 and heptene-1 in anhydrous solvents, such as hexane, carbon tetrachloride, or glacial acetic acid, the 1-bromoderivatives are exclusively obtained. With 48 per cent *aqueous* hydrobromic acid, on the other hand, the 2-bromoderivatives are produced.

The presence of peroxides affects the way in which the hydrogen bromide is added to the double bond. Thus, vinyl bromide, $\text{CH}_2 = \text{CHBr}$, in the absence of peroxides, adds on hydrogen bromide with the sole formation of 1:1-dibromoethane. In the presence of peroxides, 1:2-dibromoethane is chiefly formed (Kharasch). The course taken in the addition of a molecule to a double bond is probably determined principally by the nature of the polarization of the system containing the double bond and of the adducts.

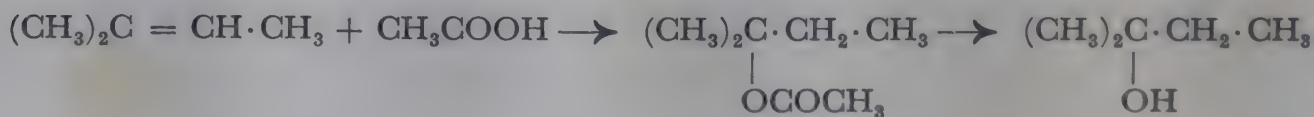
If the two unsaturated carbon atoms of the alkylene are attached to the same number of hydrogen atoms, but one of them is linked to a CH_3 group, the addition of the halogen atom takes place to the latter carbon atom (Saytzev-Wagner):



4. In an exactly similar way, other acids add on across the double bond. The rule that *the negative acidic ion adds on to the carbon atom poorer in hydrogen* holds for them also. Thus, isobutylene and sulphuric acid first give the alkyl hydrogen sulphate, which with water then decomposes into isobutyl alcohol and sulphuric acid:

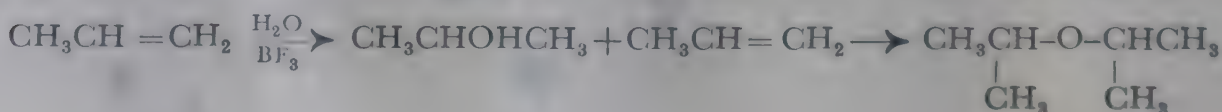


Organic acids, such as acetic acid and oxalic acid, react similarly:

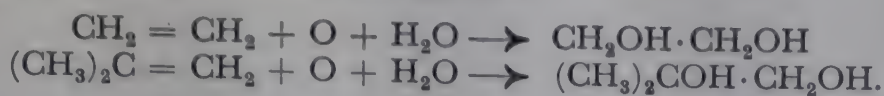


In this way it is possible to add the elements of water to an olefin and convert it into an alcohol. Ethylene is the only one to give a *primary* alcohol; all the others give *secondary* or *tertiary* alcohols.

Direct addition of water to the olefin double bond can be brought about by the use of BF_3 as catalyst. The alcohol formed may in certain cases combine, under the action of the boron fluoride, with another molecule of the olefin, to give ethers:

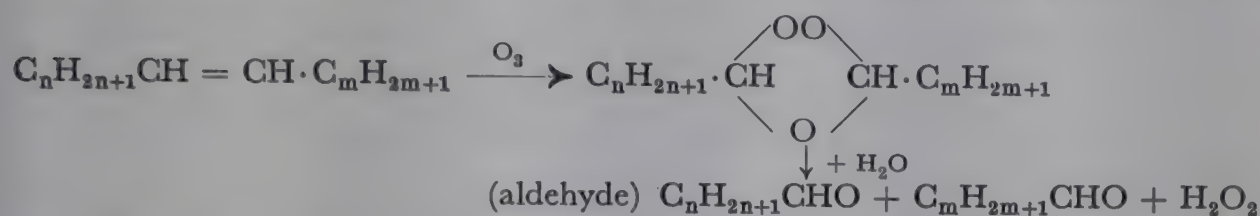


5. *Oxidizing agents* attack the alkylenes very readily. By careful oxidation, with potassium permanganate for example, it is possible to carry out the reaction so as to obtain dihydric alcohols, the glycols:



The ease with which the alkylenes react with potassium permanganate distinguishes them from the paraffins and their derivatives which are much more stable towards this reagent. Cold potassium permanganate solution is used in A. von Baeyer's method for the qualitative detection of the double bond. *Immediate decoloration of the permanganate solution indicates the presence of carbon double bonds.* The test is carried out in alkaline solution (sodium carbonate or bicarbonate), but in the case of basic substances (amines) in sulphuric acid solution.

The oxidation of olefins with *ozone* is of special importance. The gas adds on to the double bond easily and quantitatively. If the process is carried out in anhydrous solvents the explosive ozonides are produced, which, when acted upon by water, decompose into two molecules of aldehydes or ketones:



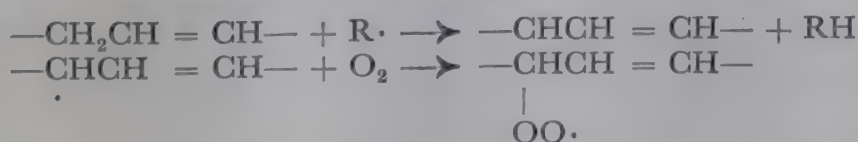
The method has been of great service in the hands of Harries in the determination of the constitution of complex unsaturated compounds. From the nature of the aldehydes and ketones formed by the hydrolytic fission of the ozonides it is usually possible to ascertain the position of the double bond in the olefin.¹ See also p. 207.

6. Osmium tetroxide adds on to olefins with formation of esters of osmic acid (I):



These can be reduced (for example with sodium sulphite) to glycols, and are decomposed by hydrogen peroxide into aldehydes and ketones. The two reactions can therefore be compared with the oxidation of the olefins by permanganate, and their fission by ozone (Criegee). Other observations show that the action of H_2O_2 and OsO_4 on olefins may also give rise to glycols.

7. Some olefins (in particular di- and polyolefins) are autoxidizable, i.e. they combine spontaneously with molecular oxygen. Mostly, hydroperoxides are thus obtained, whose formation is a result of chain reactions started by some radical ($\text{R}\cdot$). The hydroperoxide group always enters in the position next to the double bond:



¹ See C. D. HARRIES, *Untersuchungen über Ozon und seine Einwirkung auf organische Verbindungen*, Berlin, (1916). — E. FONROBERT, *Das Ozon*, Stuttgart, (1916). — M. MOELLER, *Das Ozon*, Brunswick, (1921). — ALFRED RIECHE, *Alkylperoxyde und Ozonide*, Dresden and Leipzig, (1931).

A special type of polymerization of the olefins is the combination of two molecules of the olefin with mutual saturation of the double bonds. This leads to the formation of carbocyclic compounds, which belong to the *cyclobutane* type:



Methylene. The extremely unstable methylene radical is formed by thermal decomposition of diazomethane at low pressures and at temperatures below 550°. Its formation has been demonstrated by passing the gas over a tellurium mirror, which is dissolved with the formation of $(\text{CH}_2\text{Te})_n$ (Rice, Glasebrook). The life-period of the radical is only a few thousandths of a second.

Ethylene. This hydrocarbon is present to the extent of 4–5 per cent in coal gas. Coke-oven gas is richer in the hydrocarbon, and American natural gases sometimes contains up to 20 per cent of ethylene. It can be extracted by means of concentrated sulphuric acid, being thus converted into ethyl hydrogen sulphate, from which alcohol and ether are obtained.

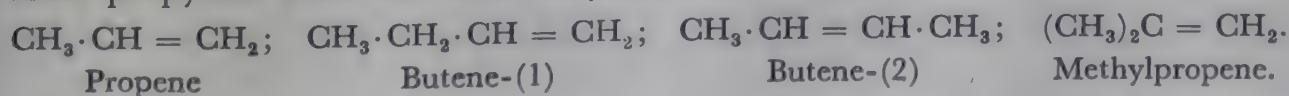
The laboratory method of preparing the gas is the dehydration of alcohol by means of concentrated sulphuric acid. Technically, as explained above, the dehydration is carried out by passing alcohol vapour over heated alumina. The partial reduction of acetylene, C_2H_2 , to ethylene, is also carried out.

Ethylene is a colourless, almost odourless gas, which burns with a luminous flame. Its melting point is -169° , boiling point -102.7° , critical temperature 13° , and critical pressure over 60 atmospheres. It is difficultly soluble in water, but dissolves somewhat better in alcohol and ether. With air and oxygen it forms explosive mixtures.

Since ethylene is a substance which is fairly easily obtained technically, endeavours have often been made to devise new uses for the gas. Relatively small quantities are used for the preparation of ethylene dichloride, and dibromide as anæsthetics, for the synthesis of glycol (ethylene \rightarrow ethylene dibromide \rightarrow ethylene diacetate), and for the preparation of ethane. The attempts to oxidize ethylene to formaldehyde by means of oxygen are of interest. By the action of very high pressures under certain conditions, ethylene can be converted into a mixture of solid polymers which are known as *polythenes* (trade name "*Alkathene*"). They consist of saturated hydrocarbons with little branching of the chains which are built up of about 1000 C-atoms. "*Alkathene*" finds practical use as an electrical insulating material, for cable insulation, and similar purposes, owing to its resistance against water.

Formerly ethylene was called "olefiant gas" or "elayl".

Higher olefins. Numerous higher homologues of ethylene have been synthesized and are also obtained as decomposition products in pyrolytic reactions. After propylene there are three butylenes and five amylenes:

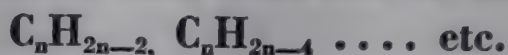


Propylene, which is available in unlimited quantities in the cracking gases of petroleum refineries, is the starting material for the production of *isopropyl* alcohol, allyl chloride, propylene chloride, and acetone, while the two normal butylenes are used for the preparation of *sec.* butyl alcohol, and methylpropene

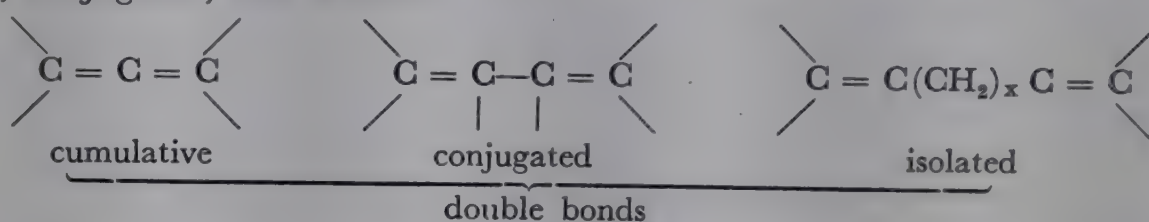
isobutylene) for the preparation of *tert.* butyl alcohol. The most important use of these olefins in the mineral oil industry, viz. the manufacture of petrols with a particularly good resistance to knocking, has already been mentioned in an earlier section.

The highest known olefins, of which the constitutions are still not clear, are obtained as decomposition products of natural substances. Thus, cerotene, $C_{26}H_{52}$, is obtained by decomposition of Chinese wax, and melene, $C_{30}H_{60}$, by the pyrolysis of beeswax, the vacuum distillation of lignin, from Montrambert coal, and Galician petroleum. Both are solid and crystalline. Cerotene melts at $57-58^\circ$, and melene at 62° .

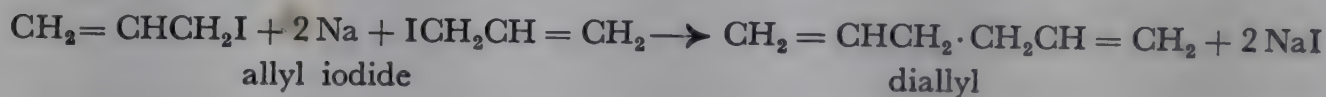
Unsaturated hydrocarbons with two or more double bonds



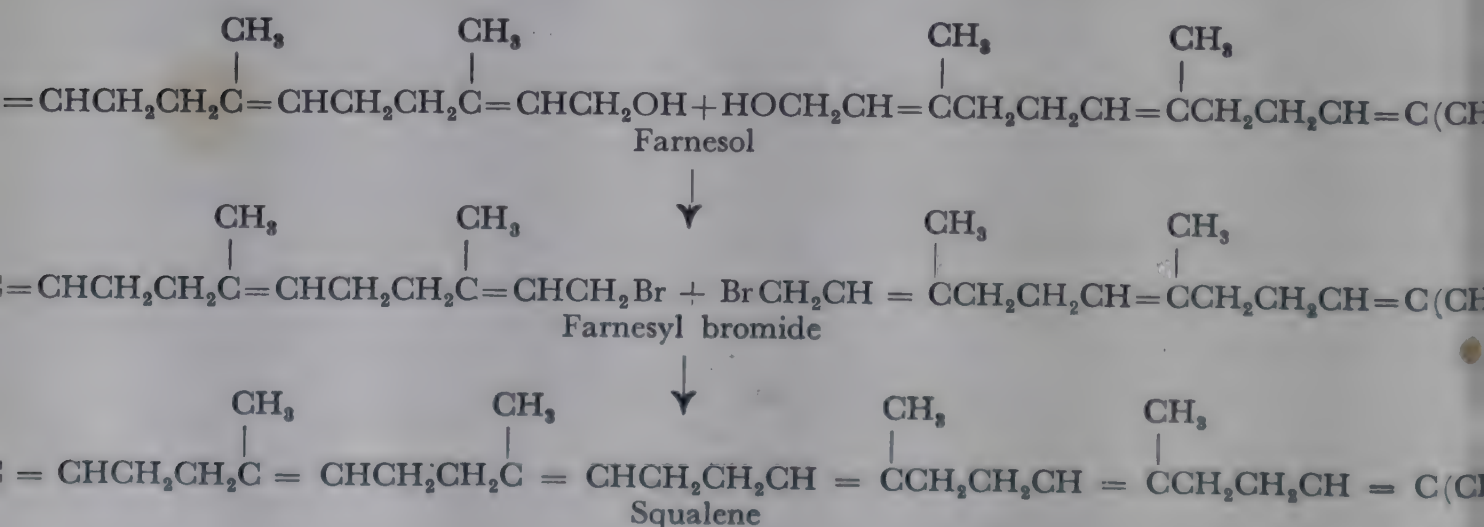
There are three different kinds of systems with two double bonds — cumulative, conjugated, and isolated.



1. **Compounds with isolated double bonds** show essentially the behaviour of simple olefins, except that here, of course, there are two double bonds across which addition can occur. Amongst the simplest representatives of this group, and the easiest to obtain, is diallyl, which is prepared by the action of sodium on allyl iodide:

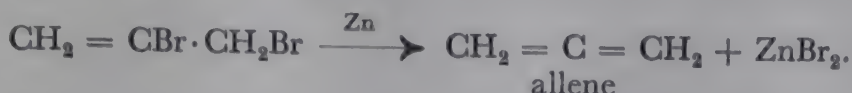


Considerable interest has been aroused in recent times by the unsaturated hydrocarbon **squalene**, $C_{30}H_{50}$, which forms a large proportion of the liver oil of certain fish (the sub-class *Elasmobranchii*) and also occurs in yeast. It is made up of six isoprene residues and contains six isolated carbon double bonds. Its constitution has been arrived at by synthesis (P. Karrer). This starts with farnesol, and proceeds through farnesyl bromide, which by the action of magnesium is converted directly into squalene:

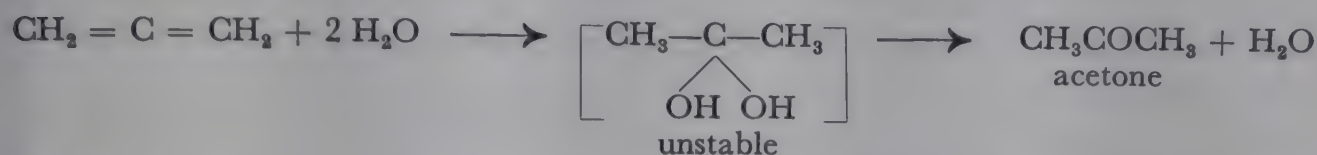


Squalene is an aliphatic triterpene (cf. the terpenes) and is also related to the carotenoids as regards constitution.

2. The simplest hydrocarbon with **cumulative or twinned double bonds** is ALLENE, $\text{CH}_2 = \text{C} = \text{CH}_2$, which is made from dibromopropylene by removing two atoms of bromine with zinc dust:



Allene is a gas, melting point -146° , boiling point -32° . If its solution in concentrated sulphuric acid is distilled with water, allene adds on water, and is converted into acetone:



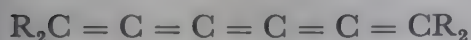
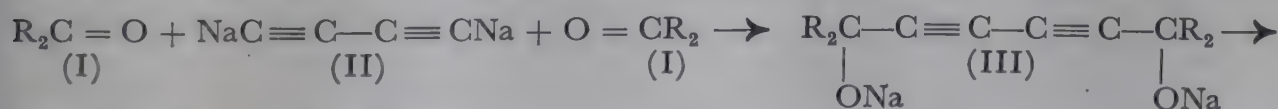
By heating with sodium (in ether) allene rearranges to methylacetylene:



A homologue of allene which is fairly easily obtained is unsymmetrical dimethylallene, $(\text{CH}_3)_2\text{C} = \text{C} = \text{CH}_2$, which gives acetone on oxidation. Water adds on in a similar way as to allene, methyl *isopropyl* ketone, $(\text{CH}_3)_2\text{CH} \cdot \text{COCH}_3$, being the reaction product.

Allene compounds have considerable interest from the point of view of stereochemistry, because it can be seen that certain substitution derivatives can exist in mirror-image isomerides (which are therefore optically active, see Ch. 4, p. 100). In the case of complicated derivatives of allene (e.g. 4-methylcyclohexylideneacetic acid, see Ch. 54), both isomerides have been prepared.

Recently, the synthesis of compounds containing several cumulative double bonds has also been achieved (R. Kuhn). They correspond to the formula $\text{R}_2\text{C} = \text{C} = \text{C} = \text{C} = \text{C} = \text{CR}_2$ and have been named *cumulenes*. It is remarkable that these substances are fairly stable. In their preparation sodium diacetylene (II) is condensed with ketones (I) to give diacetylene glycols (III), which are then reduced with vanadium-II-chloride or with chromium-II-chloride:



3. **Hydrocarbons with conjugated double bonds** are of interest in different connections. A system of conjugated double bonds is usually found to be very reactive. The hydrocarbons of this class easily add on various reagents, and tend to polymerize. Their strongly unsaturated nature is also shown in their molecular refraction, which is greater than would be expected from the existence of the two double bonds.

Molecular refraction of isoprene C_5H_8

Calculated without increment	Calculated with increment for two double bonds	Found experimentally
20.89	24.35	25.22

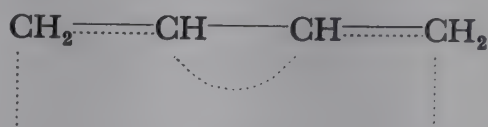
The difference is known as the exaltation due to the conjugated double bond.

Discussions of the affinity relations of a conjugated system of double bonds are of great theoretical interest. They arise from the observation that the addition of two monovalent groups to a substance with conjugated double bonds very often takes place not at one or other of the double bonds but at the *ends* of the conjugated system. Thus, butadiene is converted into 1.4-dibromobutene-(2) by the addition of two atoms of bromine:



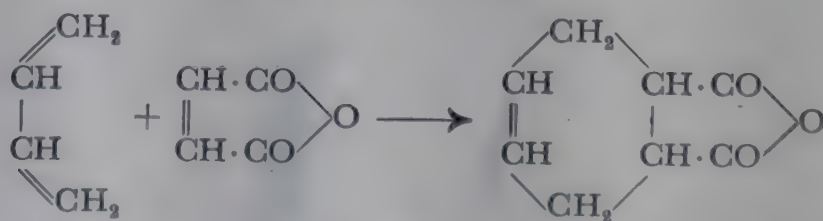
Even though the reaction does not, as Thiele at first thought, always take this course [numerous cases are known in which the addition takes place across *one* of the double bonds of the conjugated system, and even in the above case the isomeric 3.4-dibromobutene-1 (b.p.₁₄ 58–66°) is produced in addition to 1.4-dibromobutene-2 (m.p. 53°)], it has become the starting point of a stimulating hypothesis, which has been particularly valuable in the elucidation of the valency relations of benzene (see Ch. 22).

The addition to the 1.4-position of the conjugated system gave rise to the view that in such a system free partial valencies acted only at the ends. Thiele based on this the hypothesis that for two neighbouring double bonds the residual affinities of the two inner carbon atoms mutually saturated each other, as shown in the following diagram:

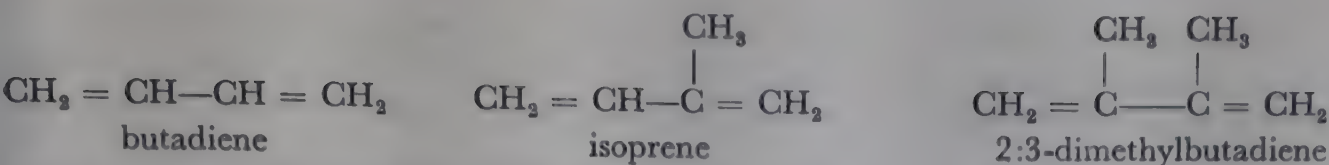


In this way the phenomenon of addition at the ends of the conjugated system was simply explained. Of course, it can also be explained, with Hinrichsen, by assuming that those compounds will be formed for which the affinity of the molecule is best compensated, and this becomes, in the case of the addition of *similar* atoms, those in which the addenda are as far apart as possible, on account of their similar polarity. Actually, too, there are many cases where addition takes place not at the ends of the conjugated system, but across one or other of the double bonds.

A very fruitful discovery as regards preparative chemistry was made by Diels and Alder when they showed that compounds with conjugated double bonds could very easily add on to quinone, maleic anhydride, maleic acid (see p. 272), and even on to ordinary ethylene compounds, such as allyl alcohol etc., the usual products being well-defined mono- or polycyclic substances (*diene-synthesis*). The reaction occurs so generally with compounds containing conjugated double bonds that it is used to detect such systems. For example, maleic anhydride and butadiene react as shown below:



Amongst hydrocarbons with conjugated double bonds three simple ones, *butadiene*, *isoprene*, and *dimethylbutadiene*



have recently assumed great importance because they yield on polymerization substances like rubber. For this reason, the methods of preparing them have been extensively studied and improved.

BUTADIENE, or ERYTHRENE is found in small amounts in coal-gas.

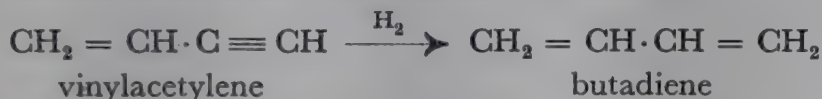
A method of preparing butadiene, due to Perkin jun., consists in chlorinating *n*-butyl chloride, and splitting off hydrogen chloride catalytically from the mixture of α,β -, α,γ -, and α,δ -dichlorobutanes produced. According to Lebedev, if alcohol vapour at high temperatures is passed over dehydrating catalysts (silica gel, alumina, etc.) it is converted, in 30 per cent yield, into butadiene:



A synthesis of butadiene of technical importance has been developed which starts from acetylene (see p. 72), converting it into acetaldehyde, aldol, and butylene glycol, butadiene being obtained from the latter by removal of water:



Further, it is possible to convert vinylacetylene (see p. 69), a polymerization product of acetylene, into butadiene by addition of hydrogen in the presence of catalysts. The process finds some application in industry:

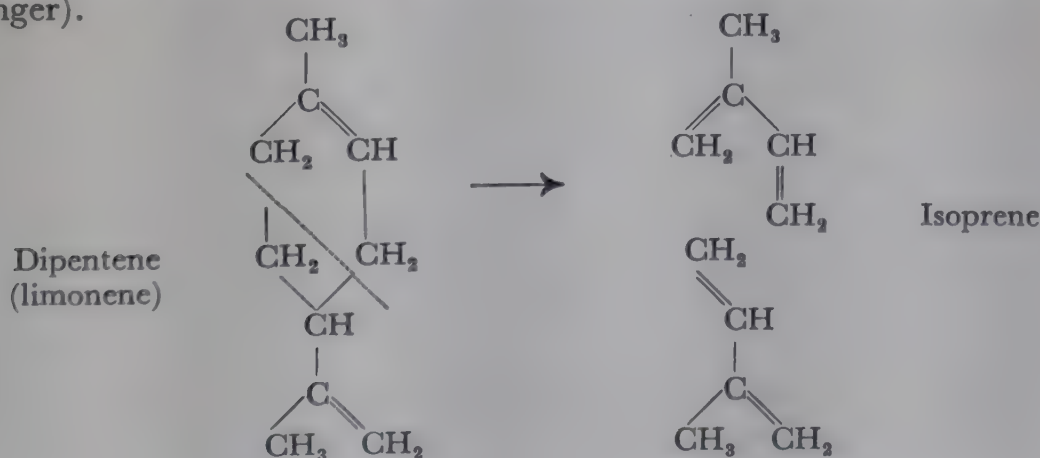


In the U.S.A., butadiene is produced from the various butanes and butenes of the cracking gases, by catalytic dehydrogenation:

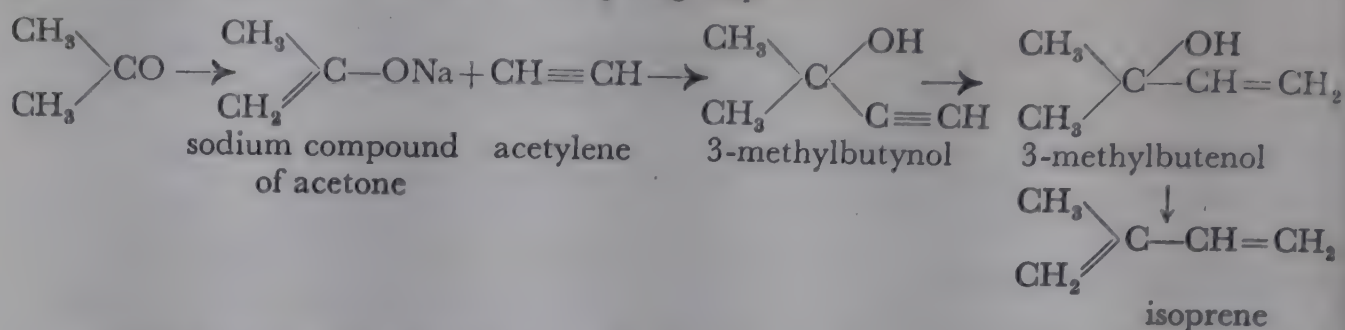


The boiling point of butadiene is $+1^\circ$. With regard to its technical application, see rubber and styrene.

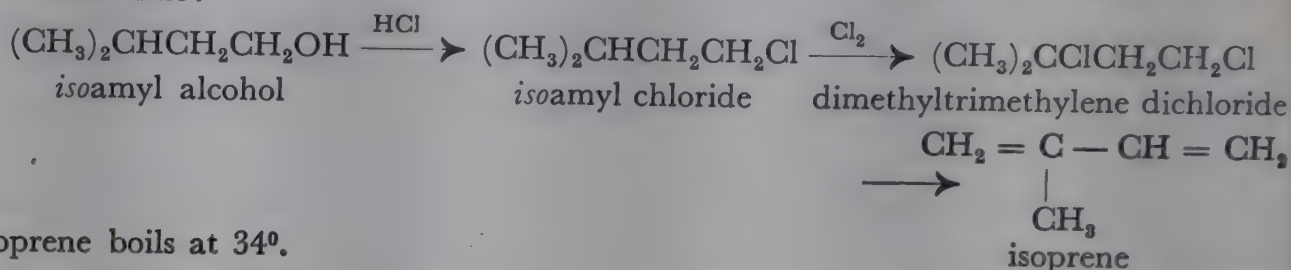
ISOPRENE is obtained by the dry distillation of natural rubber. It is formed when limonene (q.v.) or dipentene vapour, or the vapour of turpentine oil is passed over a red-hot platinum wire. The yield is particularly good when dipentene vapour is diluted with nitrogen, or is passed over the catalyst at low pressure (Staudinger).



A number of processes can be used technically to obtain this important hydrocarbon. One of them starts with acetone, CH_3COCH_3 , which, in the form of its sodium compound, is condensed with acetylene to give 3-methylbutynol. This is reduced to 3-methylbutenol, and water is removed from the latter giving isoprene:

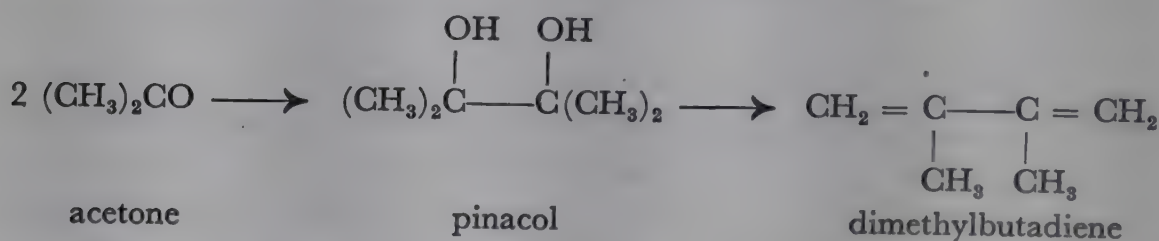


Isoamyl alcohol from fusel oil can also be used for the preparation of isoprene. It is converted by hydrogen chloride into *isoamyl* chloride, and this by chlorination into dimethyltrimethylene dichloride, which decomposes giving isoprene when passed at 470° over soda-lime:



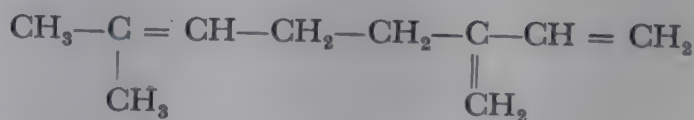
Isoprene boils at 34° .

DIMETHYLBUTADIENE is obtained technically entirely from the cheap substance acetone. Acetone is reduced to the dihydric alcohol, *pinacol* (see p. 174), and this is converted into dimethylbutadiene by removal of water:



Dimethylbutadiene is the starting point in the preparation of methyl rubber, an artificial rubber-like mass.

Of the remaining hydrocarbons with conjugated double bonds, two are worthy of mention. They are similar to terpenes and may be called aliphatic terpenes. They are *myrcene*, which occurs in various essential oils, and the isomeric compound *ocimene*. Both are derived from 2:6-dimethyloctane and contain three double bonds. Myrcene has the formula:

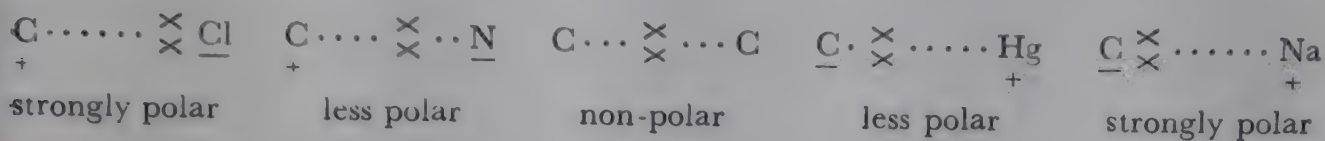


It is also contained in the dehydration products of the alcohol linalool (see p. 110).

The electronic concept of the carbon bond and the carbon double bond.

Every single, non-ionic binding is effected by means of a shared electron pair (Lewis, Heitler-London). Generally, however, this electron pair is not distributed equally between the two atoms. Only when the atoms are completely identical ($\text{H}-\text{H}$, $\text{C}-\text{C}$ in ethane, etc.) can both partners have an equal share of the doublet. In all other cases the distribution is unequal, and this imparts to the bond a polar

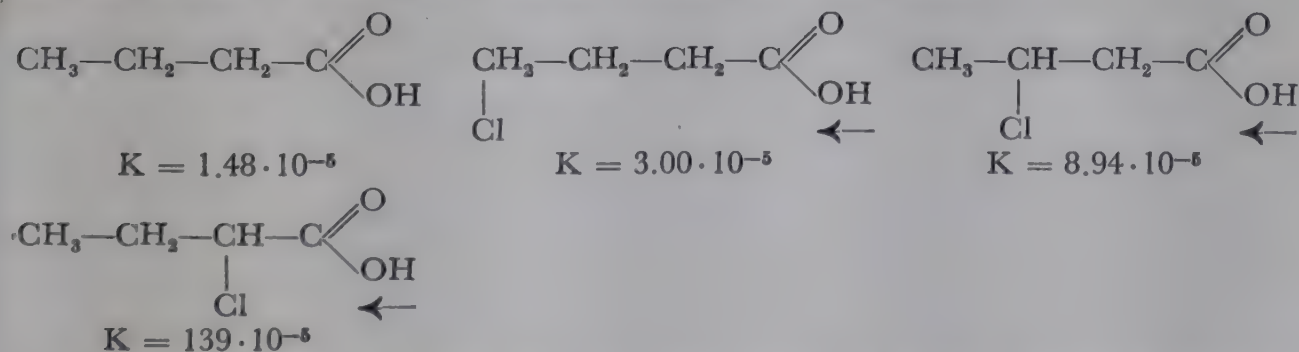
character. That atom which has the larger share of the electron pair becomes negative with respect to its partner. Such a bond is thus a small electrical dipole and is called a dipolar bond. The size of these dipoles can be obtained from dielectric measurements (Debye). Usually it is, however, possible to ascertain the orientation of the dipole without any measurements, since the more metallic of the two atoms is always its positive end. If the polarity of the bond is represented by the position of the shared electron pair on a line joining the two atoms, the following diagrams are obtained:



The individual atoms in a molecule thus differ in their polarity, and the latter can be regarded as responsible for the diverse reactivity. *The completely polarized bond is the ionic bond.*

The concept of the opposite electrical charges of the different atoms within a molecule is particularly due to Vorländer, Flürscheim, Noyes, Lapworth, Sidgwick, Robinson, Ingold, and others.

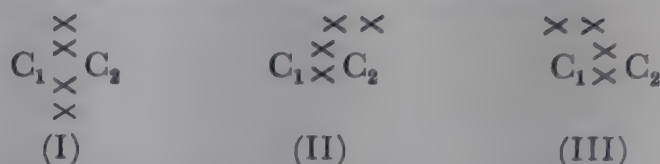
In order to simplify matters, the influence of a substituent on the reactivity of a given group of the molecule is generally considered, e.g. the influence on the acidity of a carboxyl group of an organic acid. It is fairly generally agreed to-day that the influence of the substituent is an electrostatic one. The dipole is nearly always arranged in such a way that the distance of its positive end from the reactive group is different from that of its negative end. The reactive group is thus under the influence of an electrostatic field which causes a displacement of the electrons and atomic nuclei within this group, hence leading to a change in the reactivity. For example, in the three chloro-substituted butyric acids the positive end of the $\text{C}-\text{Cl}$ dipole lies nearer to the carboxyl group than does the negative end. The carboxyl group is therefore under the influence of an electric field, which causes a shifting of the electrons in one direction (as indicated by the arrows), and of the atomic nuclei, e.g. the proton, in the opposite direction. The proton accordingly leaves the compound in question more readily than if the electric field were absent, and in consequence, the chlorobutyric acids are stronger acids than butyric acid, as may be seen from the dissociation constants below:



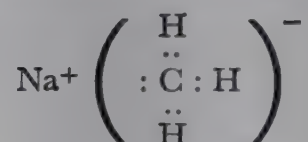
Since the strength of the field increases according as the chlorine is closer to the carboxyl group, it is obvious why the acidity increases in the order γ -, β -, α -chlorobutyric acid. This electrostatic effect of a substituent is often denoted as "general", "inductive", or "direct effect".

A special part is played in organic chemistry by the *reactivity of double bonds*.

Numerous reactions may be represented by a chain of consecutive reactions which is started by the reaction of a double bond. According to the electronic theory, the latter is represented by two electron pairs shared by the two atoms (I):

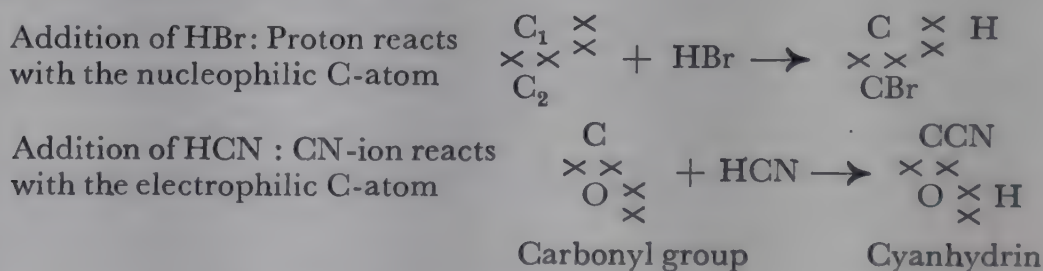


The particularly high reactivity of the double bond is due to its splitting up readily into the form II or III. In these forms one of the C-atoms has a higher electron density than the other; one of the carbon atoms has a more negative, the other a more positive character; we therefore say that such a double bond is *polarized*. The three formulæ I, II and III represent electronic isomers, or *electromers*. It is assumed that exceedingly small amounts of the forms II or III are in equilibrium with form I. However, these small amounts are very reactive and determine the course of the reaction, for the latter depends upon whether form II or form III is in equilibrium with form I. The two forms II and III react differently. Both contain an atom with an incomplete valency shell (C_1 in II, and C_2 in III). This atom must seek a reaction-partner which can give it an electron pair. Such an atom is called "electron-seeking", or *electrophilic*. Both forms also contain an atom, which, although possessing a complete valency shell, is in a similarly reactive state as, for example, the carbon atom in methylsodium:

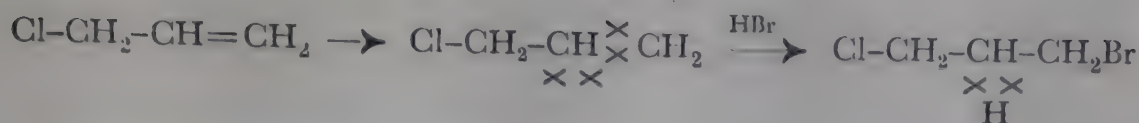


This atom seeks an atomic nucleus with which it can share its fourth electron pair, and is therefore called "nucleus-seeking", or *nucleophilic*. Such an atom combines especially frequently with the hydrogen nucleus: $\text{CH}_3^- + \text{H}^+ \rightarrow \text{CH}_4$.

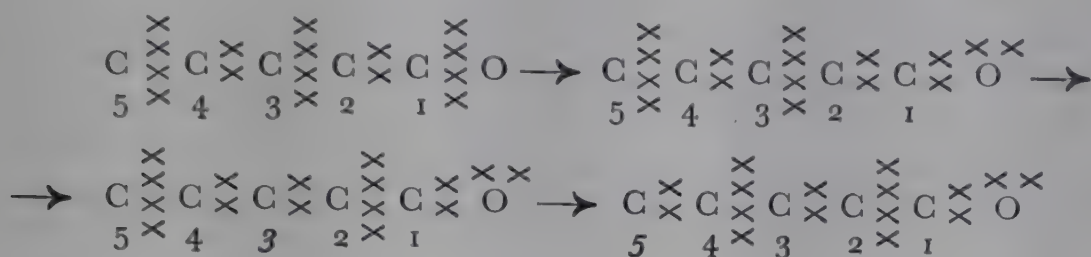
All compounds capable of reacting with double bonds may, therefore, be divided into two groups. Either they react with the nucleophilic or with the electrophilic atom of the double bond.



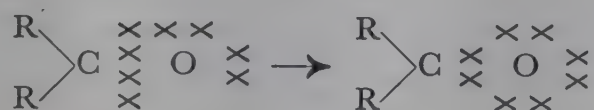
It thus makes an important difference whether the double bond in form I splits up into form II or form III, for this decides, whether, in the case of the addition of hydrogen bromide, the bromine will be attached to C_1 or C_2 . The direction which this splitting will take can be influenced by substituents. As explained above, the substituent creates an electric field covering the double bond. The electrons are affected by this, and the splitting of the double bond is favoured in one definite direction. Thus, when hydrogen bromide is added to chloropropylene, 1-bromo-3-chloro-propane is produced, because the splitting of the double bond (as indicated) appears to be the favoured one, owing to the substituent attracting the electrons:



A special situation arises in the case of a system of *conjugated double bonds*. If one of the double bonds from some cause or another, is split in a given direction, then this disproportionation is propagated through the chain of the conjugated double bonds. In the following example, the carbonyl group splits up in such a way that the oxygen acquires the electrons, since it is the less metallic partner in the bond. The fact that the carbonyl group is attached to a chain of conjugated double bonds does not imply, however, that the first carbon atom must necessarily be the electrophilic one. Owing to the propagation of the splitting shown, it may also be atom 3 or atom 5:

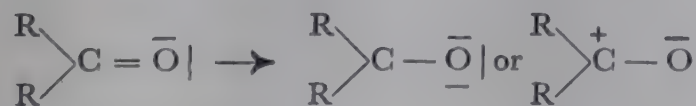


Whereas the ethylenic group, under the influence of substituents, may be polarized in either direction along the double bond, there is usually a favoured direction of the polarization in double bonds between atoms of different elements. Thus, for example, polarization of the carbonyl group always takes place in such a way that the electrons are displaced towards the oxygen, and the carbon becomes electrophilic:



In recent times it has become customary in the "electronic formulation" of organic compounds to indicate an electron *pair* by a dash. In order to distinguish, furthermore, between electron pairs which are shared by two atomic nuclei, and the so-called *lone* pairs of electrons which are attached to only one atomic nucleus, the latter are indicated by horizontal, or vertical, dashes placed around the symbol of that particular atom.

In this simplified notation the preceding formulæ appear in the following form:



If a molecule contains a group having a lone electron pair, together with a group which tends to acquire it, then this electron pair will be arranged in an intermediate position between the two extreme states. Thus, for instance, in an acid amide (see p. 223), the actual state will lie between the two limiting electronic formulæ (a) and (b):



Two such formulæ are called *mesomeric*¹, and the intermediate state existing between the two electromeric formulæ, *mesomerism*. Mesomerism should be clearly distinguished from tautomerism (see p. 109, 267); in the latter, there is a displacement of atoms, in the former, a displacement of electrons.

Hydrocarbons of the acetylene series

The simplest hydrocarbon of the acetylene series is *acetylene*, C_2H_2 . If the views which were developed in connection with ethylene are applied to acetylene, a hydrocarbon C_2H_2 can only be formulated with a "triple" bond, as shown in the formulæ I and II.

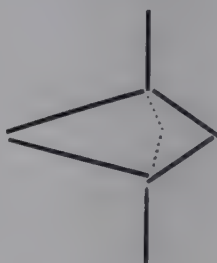


I

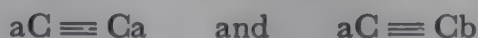


II

The formulæ agree with the known facts about acetylene. They are also intelligible from the point of view of stereochemistry, since they indicate that two carbon atoms, of which the valency forces are directed to the corners of a tetrahedron are united to each other by two tetrahedral faces:



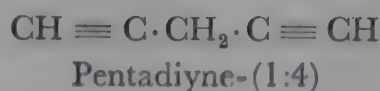
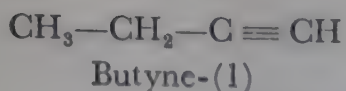
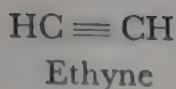
The capacity of the carbon atoms for free rotation with respect to each other is therefore excluded in acetylene. This stable arrangement of atoms is, however, not the cause of new types of isomerism, in contrast to the ethylenic double bond, for the two possible types of acetylene derivatives can only exist each in one form, as the diagram showing their spatial arrangement indicates:



Like the double bond, the triple linkage is also accompanied by an increased molecular refraction. The *increment for the acetylenic linkage* (designated by F^\equiv) in hydrocarbons amounts to 2.325–2.573, thus exceeding the increment for the carbon double bond ($\text{F}^=$ 1.73).

According to the international rules of nomenclature the acetylenic hydrocarbons are characterized by the ending *-yne*. Their general name is *alkynes*. Otherwise, the same principles hold as for the nomenclature of the paraffins and olefins:

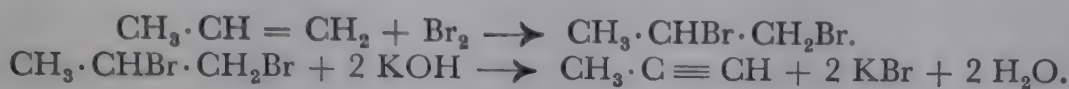
¹ See BERNDT EISTERT, *Tautomerie und Mesomerie*, Stuttgart, (1938). — WHELAND, *The Theory of Resonance*, New York and London, (1945).



Another nomenclature based on the name of the first member of the series, acetylene, is also used and is often satisfactory. Thus butyne-(1) may also be called ethylacetylene.

Methods of preparation of the acetylenic hydrocarbons. The following are general methods for the preparation of the acetylenic hydrocarbons:

1. Addition of halogen (chlorine, bromine) to an olefin, and removal of two molecules of hydrogen halide by means of alcoholic or dry caustic potash:



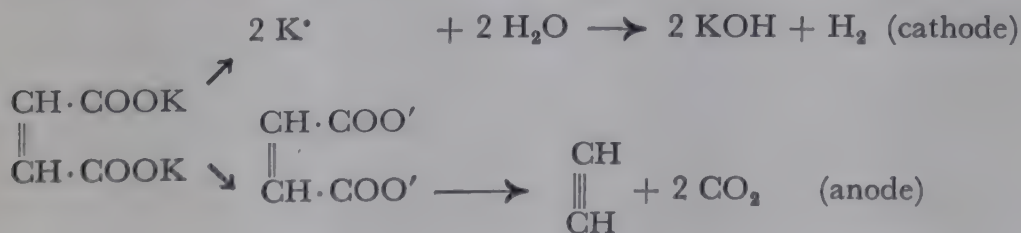
2. Aldehydes and ketones when treated with phosphorus halides are converted into halogen derivatives of saturated hydrocarbons which contain two halogen atoms attached to the same carbon atom. If these are treated with alcoholic potash, or better with sodamide, they decompose, two molecules of hydrogen halide being removed, and acetylene or its homologues being formed:



When potassium hydroxide or sodium hydroxide is used the reaction should be carried out at the lowest possible temperature, since otherwise isomerization may occur. For, monoalkylacetylenes show the peculiarity of isomerizing at high temperatures under the influence of alkali-metal hydroxides, the unsaturated linkage wandering to the inner part of the chain, giving dialkylated acetylenes (Faworski):

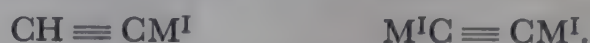


3. An interesting method of making some acetylenic hydrocarbons is the electrolysis of the alkali-metal salts of unsaturated dicarboxylic acids. It is a special case of Kolbe's hydrocarbon synthesis, which has been more fully dealt with in connection with the paraffin hydrocarbons. If, for example, the potassium salt of fumaric or maleic acid is electrolysed, hydrogen is produced at the cathode, and acetylene and carbon dioxide at the anode:



Metallic derivatives of the acetylenic hydrocarbons. Acetylene and its monoalkyl-derivatives, i.e. all alkynes having the formula $\text{R} \cdot \text{C} \equiv \text{CH}$,

show the peculiarity of being converted very easily into metallic derivatives. The hydrogen which is combined with the trebly linked carbon is replaced by the metal: $RC \equiv CM^I$. Acetylene itself, the parent substance of the series, contains two hydrogen atoms which can be substituted in this way:



Such metallic compounds are called *acetylides*. They may be regarded as a special group of carbides.

The capacity of a hydrocarbon to exchange a hydrogen atom for a metal atom is not at all limited to the unsaturated hydrocarbons of the acetylenic series. Through the work of Schorigin, Schlenk, and others, the sodium alkyls, e.g. methylsodium, CH_3Na , have been discovered. The zinc dialkyls, $Zn(C_nH_{2n+1})_2$, mercury dialkyls, $Hg(C_nH_{2n+1})_2$, alkylmagnesium salts, $Mg(C_nH_{2n+1})X$, and similar compounds, which will be more fully dealt with later, have been extensively investigated. What distinguishes the acetylides from many of these compounds, however, is the ease with which they are formed. The question has therefore been discussed as to whether acetylene is an acid, and tends to ionize. This seems, however, to occur only to a very slight degree, if at all.

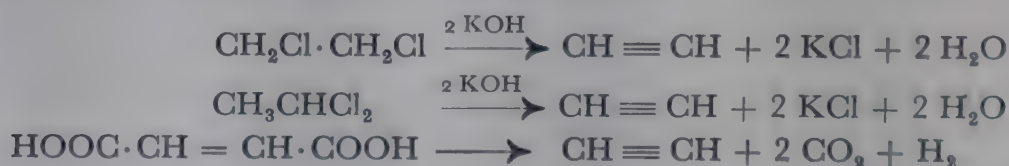
Some acetylides, such as those of the alkali metals and the alkaline-earth metals, are decomposed by water with the formation of metal hydroxides and hydrocarbons. They are very stable towards heat. Other acetylides, e.g. those of many heavy and noble metals, can only be decomposed by mineral acids. Amongst them are some which, in the dry state, are extremely sensitive towards heat and shock, and explode with great violence. This is true of the cuprous, and to a higher degree of the silver salts.

Acetylene, $CH \equiv CH$.¹ The first member of the alkynes and at the same time the most important compound of the whole series, *acetylene*, is formed in the thermal decomposition of many organic compounds. For this reason it is present in small amounts in coal-gas. Its formation by the incomplete combustion of other hydrocarbons, e.g. methane, is important.



The formation of considerable quantities of acetylene from coal-gas when a Bunsen burner strikes back is due to this reaction.

For the preparation of acetylene any one of the general methods described above can be used. The removal of hydrogen chloride from 1:2-dichloroethane, or 1:1-dichloroethane, or the electrolysis of the simplest unsaturated dicarboxylic acids (fumaric and maleic acids) yields acetylene:



The production of acetylene from hydrogen and carbon at high temperatures is of interest. According to Berthelot the gas is formed when an electric arc is

¹ J. A. NIEUWLAND and R. R. VOGT, *The Chemistry of acetylene*, New York and London. (1945).

struck between carbon electrodes in an atmosphere of hydrogen. The yield can be as much as 8 per cent of the hydrogen present.

The only method at present used practically to obtain acetylene is the action of water on calcium carbide.

Calcium carbide is obtained technically by fusing quicklime and carbon together. The temperature required is greater than 2000° (usually 2500° – 3000°) so that the process can only be carried out in the electric furnace. The reaction occurs according to the equation:



The calcium carbide thus obtained is a grey to brown mass with a crystalline fracture, and contains a number of impurities. It is rapidly decomposed by water, and the reaction proceeds smoothly with formation of acetylene:

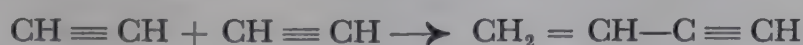


The acetylides of other alkaline-earth metals and of the alkali metals and lanthanum, all react with water in a similar way to calcium carbide giving acetylene.

Acetylene is a colourless gas, of which the critical temperature is 37° and the critical pressure 68 atmospheres. Liquid acetylene boils at -83.8° . The melting point is -81.5° . Solid acetylene vaporizes at ordinary temperatures without melting, since the boiling and melting points are so close. The pure gas is almost odourless, the repulsive smell of the technical product being due to impurities (hydrogen sulphide, phosphine, etc.).

Acetylene burns with a *strongly luminous* and *sooty* flame. Mixtures of the hydrocarbon with air are exceedingly explosive, and the limits of composition of the explosive mixtures are wide, only those mixtures containing less than 5 per cent or more than 80 per cent of acetylene being not explosive. Mixtures of the hydrocarbon with oxygen, are, of course, correspondingly more dangerous.

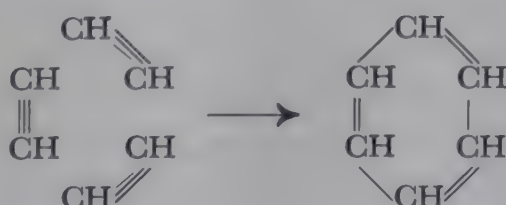
The strongly unsaturated nature of acetylene is the cause of its numerous chemical reactions. Thus, it shows a great tendency to polymerize. Nieuwland found that acetylene condensed to vinylacetylene and divinylacetylene in the presence of cuprous chloride and ammonium chloride in acid solution:



With cuprous chloride, butadiene forms the compound $\text{C}_4\text{H}_6 \cdot 2 \text{CuCl}$; acetylene, the compound $\text{C}_2\text{H}_2 \cdot 2 \text{CuCl}$; both of these are presumably formed as intermediate products during the reaction.

Vinylacetylene is of technical importance as a starting point in the preparation of rubber-like substances.

Berthelot showed earlier than this that by passing acetylene through a red-hot glass tube, benzene is formed:



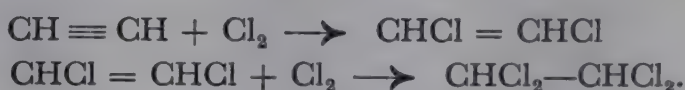
The temperature required for the polymerization can be considerably reduced if catalysts (e.g. pyrophoric iron, or nickel powder) are used. Of greater interest is the polymerization, which occurs under the influence of spongy copper, to a cork-like substance *cuprene* (Sabatier and Senderens) and *cuprene tar*. Cuprene is made up of cyclic hydrocarbons but nothing further is known of its structure. On oxidation it gives polycarboxylic acids of benzene. In cuprene tar aromatic hydrocarbons, olefins, and in smaller quantity, paraffins (hexane) have been detected.

The preparation of cuprene has been carried out recently on a technical scale. The product serves as a basis for explosives.

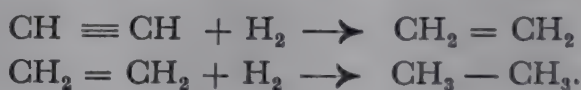
Another method of bringing about the polymerization of acetylene is to pass a silent electric discharge through the gas. At low temperatures a very unstable oil is formed, which soon becomes solid owing to polymerization. The oxidation of this compound gives aromatic substances (benzoic acid and phthalic acids).

As an unsaturated substance, acetylene enters largely into addition reactions. For the saturation of the triple linkage four monovalent atoms or groups are necessary. These are added in two steps, the first leading to derivatives of ethylene, and the second to derivatives of the saturated paraffins.

Thus the addition of chlorine to acetylene gives first dichloroethylene, which very rapidly takes up a further quantity of chlorine being converted into tetrachloroethane.

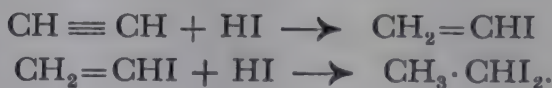


Hydrogen, if activated by a catalyst (platinum, nickel, etc.) adds on to acetylene in two stages. Ethylene is formed first, then ethane.

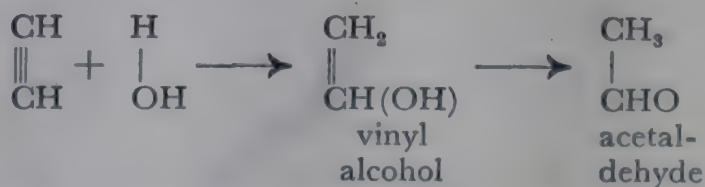


Small quantities of other hydrocarbons of the aliphatic and aromatic series are also formed as by-products.

The halogen hydracids also add on in stages:



The addition of water to acetylene has been known for some time, but has only been applied technically for about 30 years. The reaction occurs readily if the acetylene is adsorbed on freshly heated charcoal, and this is heated with water in a closed vessel. The unstable vinyl alcohol is first formed, and then gives acetaldehyde:



The addition of water to acetylene takes place with good yield and in an industrially applicable form, only when *mercury salts* are used as *catalysts*. According to the process of N. Grünstein, acetylene is passed into a solution of mercuric

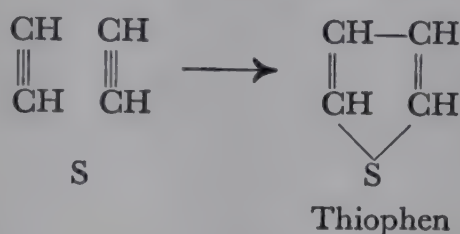
oxide in concentrated sulphuric acid at a temperature below 50°, whilst the *Konsortium für elektrochemische Industrie* uses a hot solution of mercuric oxide in dilute sulphuric acid (not more than 6 per cent acid) into which the gas is passed. The characteristic catalytic effect of the mercuric salts probably depends on the fact that mercury derivatives of acetylene are first formed, which are later acted upon by the acid forming acetaldehyde and a mercury salt. The method is used to-day for the technical production of acetaldehyde and its further transformation products (acetic acid, acetone, alcohol).

According to another process, satisfactory yields of acetaldehyde can also be obtained if a mixture of acetylene and water vapour is passed at high temperatures over specially prepared catalysts, particularly derivatives of ferric oxide, or over contact masses impregnated with phosphoric acid and heavy metals.

Nitrogen and acetylene may be made to combine to give hydrogen cyanide by passing electric *sparks* through the mixture of gases:



If acetylene is passed over iron pyrites at 280°–310° the sulphur from the pyrites combines with the acetylene, and the product contains considerable quantities of the cyclic compound thiophen, together with other substances (Steinkopf):



Amongst the *metallic derivatives of acetylene* the copper and silver salts must be mentioned. They are obtained as insoluble precipitates when acetylene is passed into an ammoniacal cuprous solution, or an ammoniacal silver solution. Cuprous acetylide (C_2Cu_2) is reddish brown, and silver acetylide (C_2Ag_2) is white, but darkens in the light. Both are very explosive in the dry state, especially the silver compound, which can even explode when it is touched. Because of the insolubility of cuprous and silver acetylides they are used to detect small amounts of acetylene in other gases, for example, in coal-gas. No less explosive is mercury acetylide, which is obtained by passing acetylene into an alkaline solution of potassium mercuri-iodide:



The preparation and importance of calcium carbide as a source of acetylene have already been mentioned. The technical process of heating together calcium oxide and carbon is unsuitable for the preparation of chemically pure calcium carbide. For this purpose metallic calcium or calcium hydride is heated with carbon. Pure calcium carbide forms colourless, transparent crystals.

The alkali-metal acetylides are obtained by passing dry acetylene over the warm metals. First one, then the second hydrogen atom is replaced:



Recently alkali-metal acetylides have often been used for the introduction of the acetylene residue into other compounds.

In the last decades acetylene has become an important technical product, and has found numerous new applications. As regards illumination, it is, however, only used for lighting on a small scale, though it is of great importance in this connection (mines, bicycle lamps). Its explosive properties and the development of the electric lamp have prevented its further use for lighting purposes. On the other hand, it has found a new application in the oxy-acetylene flame for the autogenous welding of metals. It is often sold as a solution in acetone, soaked up in some porous substance, in steel cylinders ("dis-sous-gas"), since in this form it shows the least tendency to explode. From acetylene, acetaldehyde is technically produced by the addition of water, as mentioned above. From this, acetic acid, acetic anhydride, acetone, and alcohol can be prepared. Various chloro-derivatives of acetylene are used as solvents, and to a certain extent, as substitutes for camphor (e.g. hexachloroethane). From the addition products of acetone with acids, alcohols, and amines, artificial resins and other synthetic substances are produced by polymerization. Within the last few years acetylene has been used to make butadiene (see p. 61) from which artificial rubber (see Ch. 56) is obtained. The fact that acetylene has the properties of a narcotic has led to its use in medicine, where it is employed under the name *narcylene* for producing narcosis. For this purpose it must be purified, and particularly must be free from hydrogen sulphide and phosphine, impurities found in all crude acetylene made from technical calcium carbide. Finally, acetylene finds a limited use in the manufacture of lamp-black (acetylene black).

CHAPTER 3

THE MONOVALENT HALOGEN FUNCTION: ALKYL HALIDES, ALKYLENE HALIDES

By the term "*functions of the hydrocarbons*" is to be understood compounds which are derived from hydrocarbons by the replacement of hydrogen by other atoms or groups. If only one hydrogen atom of a hydrocarbon is substituted, the function is called monovalent; if two substituents are attached to the *same* carbon atom, it is a divalent function, and similarly for tri- and tetra-valent functions.

Alkyl halides

The *monovalent halogen function* is of special importance in aliphatic chemistry since the alkyl halides are easily obtainable, and on account of their great reactivity are valuable as starting substances for many syntheses.

Methods of preparation. The formation of the alkyl halides by direct chlorination and bromination of the paraffin hydrocarbons has, with the exception of the chlorination of methane, and more recently of pentane, only theoretical interest, as the reaction often does not proceed in a straightforward manner, but gives rise to a mixture of different compounds halogenated to various extents. Iodine can not be introduced at all into the molecule in this way.

More important from the preparative point of view is the formation of the alkyl halides by the addition of the hydrogen halides to the olefins. As stated above, the rule is that the halogen atom attaches itself in preference to the carbon atom which has the least hydrogen:



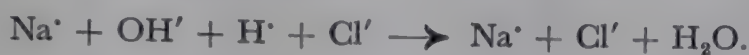
The most usual method of preparing the alkyl halides is the replacement of the hydroxyl group of an alcohol by halogen. This can be done by the action of the concentrated halogen acids on the alcohol:



The reaction corresponds formally to the formation of a salt from an acid and a base:



There is, however, a difference between the two processes. Bases and acids are largely dissociated; when they come together hydrogen ions and hydroxyl ions combine almost at once to give the very little electrolytically dissociated water, so that the reaction which really occurs is



Ionic reactions always occur instantaneously.

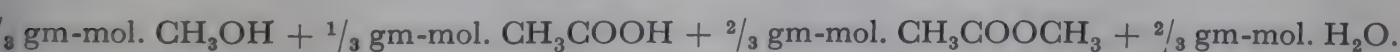
The reaction between alcohol and hydrogen halides is governed by other laws. Alcohol is exceedingly little ionized. For the removal of the hydroxyl group a certain time is required. The reaction between alcohol and acid, with elimination of water, known as *esterification*, is therefore a time reaction. Esterification is never complete, since a second process goes on at the same time, the fission of the alkyl halide formed by the water present. The process of ester formation is *reversible*:



There is a dynamic equilibrium between the four substances, the velocities of the two opposing reactions having become equal.

The equilibrium state is only reached after some days at ordinary temperatures, but when heated, the equilibrium is attained in a much shorter time, for instance after a few hours. It depends little on the nature of the alcohol and the acid, but essentially on the proportions of the substances brought together in the reaction.

For example, if equivalent weights of substances are used, e.g. 1 gm-mole of alcohol and 1 gm-mole of acetic acid, or 1 gm-mole of ester and 1 gm-mole of water, after a sufficiently long time an equilibrium state is reached in which the composition of the homogeneous system is



The equilibrium concentrations are, however, different if the quantities of the reacting substances are different. The conditions are governed by the Law of Mass Action, and for this case of esterification the following relationship holds:

$$k' [\text{CH}_3\text{OH}] [\text{CH}_3\text{COOH}] = k'' [\text{CH}_3\text{COOCH}_3] [\text{H}_2\text{O}],$$

where k' is the velocity constant of the reaction between the alcohol and the acid, k'' is that of the reaction between the ester and water, and the symbols in square brackets stand for molecular concentrations.

Alkyl radical	Chloride			Bromide			Iodide		
	b.p.	m.p.	sp.gr.	b.p.	m.p.	sp.gr.	b.p.	m.p.	sp.gr.
Methyl	-23.7°	-103.6°	0.952 (0°)	+ 4.5°	- 96.8°	1.732 (0°)	+ 45°	- 66.1°	2.293 (18°)
Ethyl	+12.2°	-140.8°	0.918 (8°)	+38.4°	-119.0°	1.468 (13°)	+ 72.8°	-110.9°	1.944 (14°)
<i>n</i> -Propyl	+46.5°	-122.5°	0.912 (0°)	71°	-109.8°	1.383 (0°)	+102.5°	-101.4°	1.786 (0°)
<i>n</i> -Butyl (primary)	78°		0.907 (0°)	101°		1.305 (0°)	130°		1.643 (0°)
<i>n</i> -Amyl (primary)	107°		0.901 (0°)	129°		1.246 (0°)	156°		1.543 (0°)
<i>n</i> -Hexyl (primary)	134°		0.892 (16°)	156°		1.193 (0°)	182°		1.461 (0°)
Cetyl, C ₁₆ H ₃₃ Myricyl, C ₃₁ H ₆₃	<289°	+64.5°	0.8412 (12°)		15° 67°		211° (15 mm)	+22° +70°	1.1347 (18°)

If 1 gm-mole of acid is mixed with m gm-moles of alcohol and n gm-moles of water (or ester) the equilibrium state is given by the more general equation:

$$k'(1-x)(m-x) = k''(n+x)x,$$

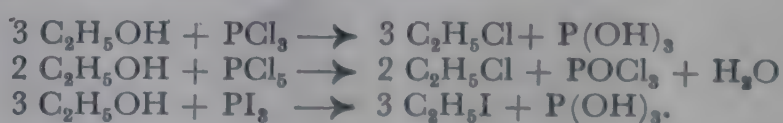
where x is the number of moles of alcohol (and obviously also of acetic acid) which have reacted. In the foregoing example is $m = 1$, $n = 0$, $x = \frac{2}{3}$.

It follows from these considerations that the yield of ester will be greater, the greater is the molecular concentration of alcohol and acid, and the more completely the water and the ester are removed. Any state of equilibrium can be displaced by changing the concentration of one of the substances participating in the equilibrium. The substance removed is formed afresh, and the reaction proceeds in such a direction as to attempt to annul the effect of the disturbance.

These considerations show how the process of esterification must be carried out practically to obtain satisfactory yields of the alkyl halides and to use up the alcohol and hydrogen halide as completely as possible. It is necessary to ensure that water shall be removed as completely as possible from the reaction mixture. This is done by using anhydrous alcohol and hydrogen halide. In many cases it is advantageous to remove the water formed during the reaction by the addition of a dehydrating agent, such as sulphuric acid, or zinc chloride. Carried out under these conditions, the esterification of alcohols with hydrogen halides is a good method of preparing the alkyl halides.

Compounds formed by the elimination of water from alcohols and acids are called *esters*. *The alkyl halides are esters of the hydrogen halides.*

Another method which is often used to replace the hydroxyl group of the alcohol by halogen is the action of the phosphorus halides on alcohols. Phosphorus tri- and pentachloride are used for the introduction of chlorine, phosphorus pentabromide and tri-iodide for the preparation of alkyl bromides and iodides, respectively.



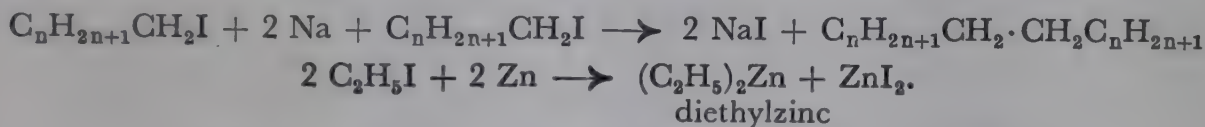
The reactions occur quickly and smoothly. They are occasionally accompanied by side-reactions, giving rise to the formation of esters of phos-

phoric acid, but these hardly affect the usefulness of the method. Instead of using the phosphorus pentabromide and tri-iodide directly, ready prepared mixtures of red phosphorus and bromine or iodine can be substituted.

Properties of the alkyl halides. The lower members are colourless gases, then follow liquid homologues. The highest are solid at room temperature. In the pure state all the alkyl halides are colourless. In consequence of a small amount of decomposition, which is promoted by exposure to light, the iodides soon become coloured red to brown. The smell of the lower alkyl halides is sweetish. They burn with green-edged flames. They are almost insoluble in water, but the liquid members are completely miscible with many organic liquids, such as ether and alcohol.

The halogen atom of the alkyl halides can be replaced by other groups comparatively readily. Since silver nitrate reacts very slowly at room temperature it is concluded that the alkyl halides are not at all, or at the most very little ionized. On warming, however, there is a rapid precipitation of the silver halide. In general it is found that iodine is more easily split off than bromine, and the latter more readily than chlorine. On account of their greater reactivity the alkyl iodides are specially suitable for syntheses. The length of the carbon chain affects the mobility of the halogen atom. The latter decreases with increasing size of the alkyl halide molecule.

Of the chemical reactions of the alkyl halides, those which give rise to the paraffins, or to substances from which the latter can be obtained, have already been mentioned. These reactions include those with sodium, silver, zinc, or magnesium.



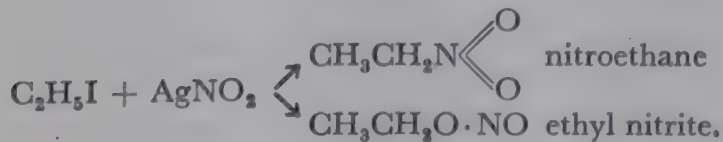
The alkyl halides can also be used in the preparation of many esters by making the halides react with salts of the acids concerned. From silver nitrate and alkyl halide, *alkyl nitrates* are obtained:



With potassium cyanide, esters of hydrocyanic acid, known as *nitriles* (and isonitriles, see pp. 187, 189) are obtained:



With potassium hydrogen sulphide the alkyl halides give *thioalcohols* (mercaptans); with moist silver oxide they are hydrolysed to *alcohols*; and with silver nitrite, they give *nitro-compounds*, and *esters of nitrous acid*.



These few examples show how valuable the alkyl halides are for organic syntheses.

Since the iodine can be removed more easily from an alkyl iodide than the chlorine from the chloride, or the bromine from the bromide, it is sometimes necessary to convert the alkyl chloride or bromide into the iodide. This method of obtaining the alkyl iodide is sometimes easier than the direct iodination of aliphatic compounds.

The replacement of chlorine and bromine by iodine may be effected by heating the compound with potassium, sodium, or calcium iodide, either in absence of a solvent, or in water, acetone, or alcohol.

The reverse reaction, the replacement of iodine by chlorine or bromine usually takes place when the alkyl iodide is heated with the chlorides or bromides of copper, silver, mercury, tin, lead arsenic, and antimony. In some of these reactions, however, mixtures of different halogen derivatives are obtained.

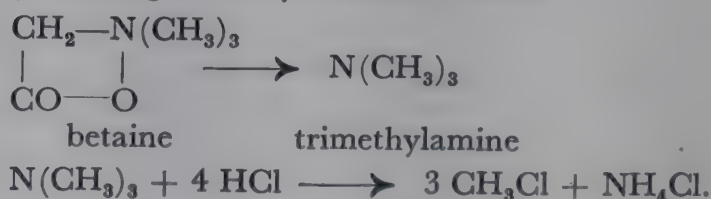
Cl can be replaced by Br by means of aluminium bromide, or bromine and iron.

Cl	„	„	„	I	„	„	„	} sodium, potassium, or calcium iodide.
Br	„	„	„	I	„	„	„	
Br	„	„	„	Cl	„	„	„	antimony pentachloride.
I	„	„	„	Br	„	„	„	copper bromide.
I	„	„	„	Cl	„	„	„	mercuric chloride.
I	„	„	„	F	„	„	„	silver fluoride, mercuric fluoride.

It is noteworthy that the primary alkyl halides can be converted into secondary and tertiary compounds. This transformation occurs, for example, in the case of propyl iodide simply on heating.

This rearrangement is accelerated considerably by the presence of aluminium chloride or bromide. It is therefore often found that the products obtained when an alkyl halide reacts in the presence of aluminium chloride are not derivatives of the alkyl halide *used*, but of an isomeric form (with secondary or tertiary alkyl radicals). See also the Friedel-Crafts reaction, Ch. 23.

METHYL CHLORIDE, CH_3Cl . This compound is prepared technically by the esterification of methyl alcohol with hydrochloric acid. The residual liquors from beet-sugar molasses, which are rich in betaine (see p. 294) are also a source of methyl chloride. The liquor ("wash") is decomposed by dry distillation at about 300° , and the trimethylamine thus formed is decomposed into methyl chloride and ammonium chloride by heating with hydrochloric acid:



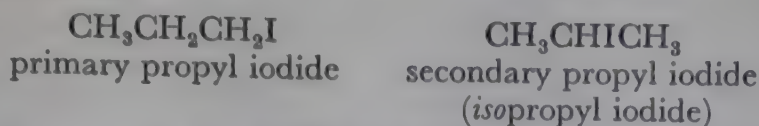
Methyl chloride has found a limited use as a methylating agent in the manufacture of dyes. It is used in the production of low temperatures, and occasionally in medicine as a local anæsthetic. When placed on the skin its evaporation produces intense cold, accompanied by insensibility of the part concerned.

METHYL IODIDE, CH_3I , a mobile, aromatic sweetish smelling liquid, has attained special importance in organic syntheses, since its iodine atom is very reactive, and the fact that it is a liquid makes it easier to use than the chloride or bromide which are both gases at room temperature.

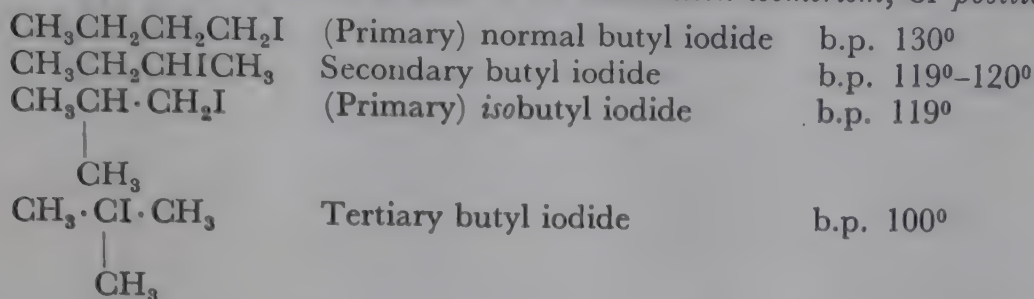
ETHYL CHLORIDE, $\text{C}_2\text{H}_5\text{Cl}$, AND ETHYL BROMIDE, $\text{C}_2\text{H}_5\text{Br}$, are both used as ethylating agents and as anæsthetics.

HIGHER ALKYL HALIDES. The monohalogen derivatives of propane and all the

higher paraffin hydrocarbons occur in isomeric forms, in which the position of the halogen is different. There are *primary*, *secondary*, and *tertiary alkyl halides*, according as the halogen atom replaces the hydrogen atom attached to a primary, secondary, or tertiary carbon atom:



This type of isomerism is known as *substitution isomerism*, or *position isomerism*.



ALKYL FLUORIDES. For the preparation of alkyl fluorides silver fluoride is treated with an alkyl iodide. Sometimes, but less often, the fluorides of mercury or antimony may be used in place of the silver salt.



Also the addition of HF on to the double bond of olefins is possible.

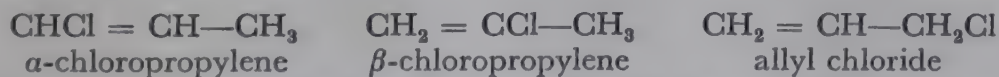
In more recent times many aliphatic fluorine compounds have been obtained by treating chlorine compounds with hydrogen fluoride in the presence of catalysts (SbCl_5 , PCl_5 , etc.), if necessary under pressure. Thus, carbon tetrachloride, on treatment with hydrogen fluoride and antimony pentachloride gives CCl_3F and CCl_2F_2 , which are used as refrigerants. Aliphatic poly-chloro-derivatives will exchange individual chlorine atoms for fluorine by the action of antimony trifluoride and mercuric fluoride. For example, the mixed substitution products $\text{CHCl}_2 \cdot \text{CCl}_2\text{F}$ and $\text{CHCl}_2 \cdot \text{CClF}_2$ are obtained from $\text{CHCl}_2\text{CCl}_3$.

METHYL FLUORIDE is a colourless gas, b.p. -78° (742 mm).

ETHYL FLUORIDE boils at -32° under atmospheric pressure. It is fairly soluble in water and burns with a blue flame. The alkyl fluorides are poisonous.

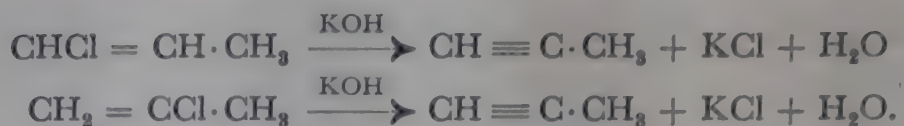
Monohalogen derivatives of unsaturated hydrocarbons

In the halogen derivatives of the unsaturated hydrocarbons the halogen can be attached either to one of the carbon atoms linked with a *multiple* bond, or to one having a *single* bond. Thus, the following chloro-compounds are derived from propylene:



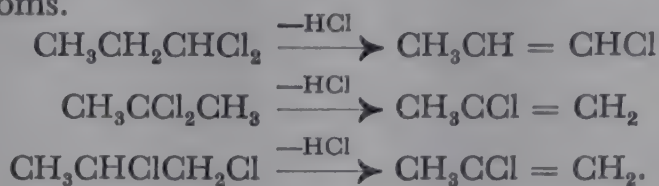
The reactivity of the three products is very different. In *allyl chloride* the chlorine is as mobile as in the alkyl halides. It can easily be replaced by other groups (OH , NH_2 , CN , etc.). Allyl chloride is therefore a suitable starting point for the synthesis of compounds of the general type $\text{CH}_2 = \text{CH} \cdot \text{CH}_2\text{X}$, which are called allyl derivatives. The radical $\text{CH}_2 = \text{CH} - \text{CH}_2 -$ is called *allyl*.

The halogen atom linked at a double bond or acetylenic linkage behaves differently. It is more inert as regards reactivity, and cannot usually be replaced in the normal manner. When any reaction takes place it leads to the splitting off of halogen hydride and formation of an acetylenic hydrocarbon. α -Chloropropylene and β -chloropropylene, for example, are converted into methylacetylene (allylene) on treatment with alkali or a tertiary amine:



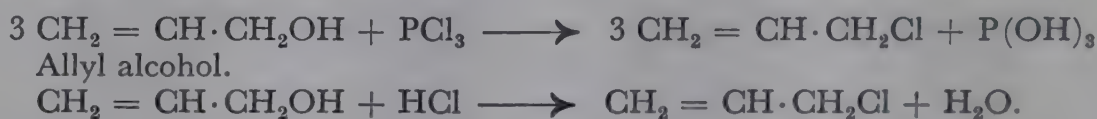
The small mobility of the halogen atoms which are attached to unsaturated carbon atoms is a general phenomenon in organic chemistry. It will be met with later in a very similar connection with the derivatives of benzene.

For the *preparation* of the monohalogen derivatives of olefins, a suitable reaction is the elimination of one molecule of halogen hydride from dihalogen derivatives in which both halogen atoms are attached to the same, or to neighbouring carbon atoms.

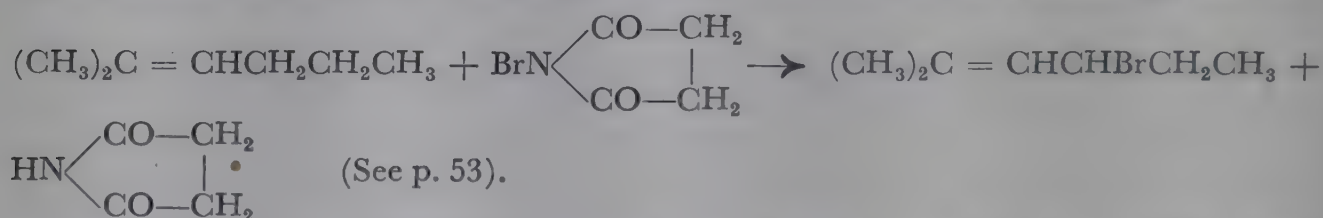


The removal of the hydrogen chloride may be carried out by the moderated action of alcoholic potash or a tertiary amine.

Those alkylene halides of which the halogen is not attached to a carbon atom itself linked with a double bond can be produced by the same methods as the alkyl halides. Thus, allyl chloride can be made from the unsaturated allyl alcohol by the action of the phosphorus chlorides or by esterification with hydrogen chloride.



Olefins which contain next to the carbon double bond a CH_2 -group activated by it, can sometimes be brominated in the methylene group, by means of N-bromosuccinimide, without any simultaneous addition of bromine to the double bond. This method, found by K. Ziegler, may be illustrated by the following reaction:



The monohalogen substitution products of acetylene of the type $\text{XC} \equiv \text{CH}$ are unstable, spontaneously inflammable and explosive. The bromine compound is formed from dibromoethylene and dilute alcoholic soda.



Dichloroacetylene, $\text{ClC} \equiv \text{CCl}$, which can be made, for example, by passing the vapour of trichloroethylene over solid caustic potash at 130° , inflames on exposure to air with explosion. It is a colourless, mobile liquid, boiling at 29° .

Better known, and more fully investigated are the halogen derivatives of the homologues of acetylene: $\text{CH} \equiv \text{C} \cdot \text{CH}_2\text{X}$ $\text{X} \cdot \text{C} \equiv \text{C} \cdot \text{CH}_3$
"propargyl" halides allylene halides

of which the members of the first group, the "propargyl" halides, are readily obtainable by the action of phosphorus halides on propargyl alcohol:



The bromine in propargyl bromide is readily mobile and replaceable.

VINYL CHLORIDE, $\text{CH}_2=\text{CHCl}$, a colourless gas, and VINYL BROMIDE, a liquid with an ethereal smell, polymerize on exposure to sunlight and in the presence of peroxides. Vinyl chloride is obtained from acetylene and hydrochloric acid in the presence of mercury salts:

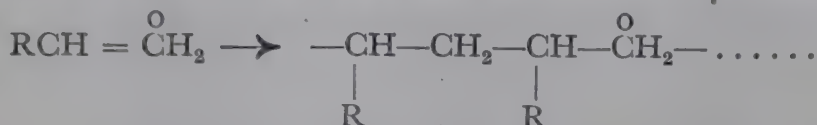


This process is at present used technically for the preparation of this product which is a valuable product in the manufacture of plastics. The plastics igelite, and vinylite, for example, are polymerization products of vinyl chloride. They are used for insulating cables, making X-ray films, foils, etc.¹

The radical $\text{CH}_2=\text{CH}\cdot$ is known as "vinyl".

All compounds containing the vinyl group $\text{CH}_2=\text{CH}\cdot$ show a great tendency to polymerize. As starting materials for the preparation of artificial resins the following substances, e.g. are also technically used in addition to vinyl chloride: vinyl ester $\text{CH}_2=\text{CHOCOR}$, vinyl ether, isobutylene $\text{CH}_2=\text{C}(\text{CH}_3)_2$, styrene $\text{CH}_2=\text{CHC}_6\text{H}_5$, and acrylic acid ester $\text{CH}_2=\text{CHCOOR}$. (Vinyl ether and vinyl ester are easily produced technically by the addition of alcohol, with KOH as catalyst, or by the addition of acids to acetylene.) As polymerization catalysts are used light, hydrogen peroxide (for the polymerization of vinyl esters and acrylic acid compounds), or sulphuric acid, boron fluoride, stannic chloride (for vinyl ether, isobutylene, etc.).

The process of polymerization² may be supposed to take place through the activation of a molecule by absorption of energy, e.g. by reaction with the catalyst or absorption of light quanta. The activated atom then adds a second molecule which is thus also activated, and so on.



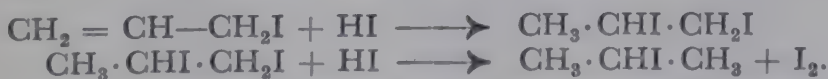
This chain reaction may finally be arrested by ring-closure of the two molecule ends, or by the uniting of two chains, or by the action of foreign substances.

This interpretation of the reaction mechanism is, for example, supported by the fact, that lower polymers when isolated and no longer in an activated state are not capable of further polymerization, and moreover, that the average number of monomers in a polymerized molecule is smaller according as more peroxide catalyst is used in the reaction.²

ALLYL CHLORIDE, ALLYL BROMIDE, and ALLYL IODIDE have also gained considerable importance. The ease with which they are made, and their great reactivity makes them suitable substances to use for the introduction of the allyl group into other compounds. Allyl iodide is obtained from glycerol by the action of phosphorus and iodine (A. Claus, and others).



Certain reaction conditions, however, must be observed. In other cases the reaction may lead to isopropyl iodide. The latter compound is formed because allyl iodide easily adds on a molecule of hydrogen iodide, and the propylene di-iodide thus formed is reduced to isopropyl iodide:



Allyl chloride boils at 46°, allyl bromide at 71°, and the iodide at 103°.

Some allyl derivatives prepared from the allyl halides (diallylbarbituric acid, or dial, allyl salicylate, allyl cinnamate) are used in medicine.

¹ W. HUNTENBURG, *Chemie der organischen Kunststoffe*, Leipzig, (1939).

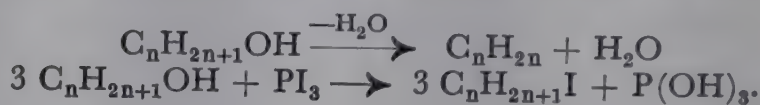
² H. MARK, *Physical Chemistry of High Polymeric Systems*, New York, (1940). — H. MARK and R. RAFF, *High Polymeric Reactions. The Theory and Practice*, New York, (1941).

CHAPTER 4

THE MONOVALENT HYDROXYL FUNCTION: MONOHYDRIC ALCOHOLS

The monohydric alcohols are derived from the hydrocarbons by replacement of a hydrogen atom by the hydroxyl group. The hydroxy-derivatives of the paraffin series thus correspond to the formula $C_nH_{2n+1}OH$. The presence of a hydroxyl group in the alcohols can be proved in a number of ways:

One hydrogen atom is different from all the others in the molecule of the alcohol, since it can be replaced by a metal, e.g. sodium. It is known that this property chiefly occurs with hydrogen atoms which are directly linked with oxygen. In agreement with this, the active hydrogen atom disappears when reactions occur resulting in the elimination of the oxygen atom of the alcohol. This is the case, for example, when one molecule of water is removed from the alcohol, the latter being converted into an olefin, or when the phosphorus halides react with the alcohol, and the hydroxyl group is replaced by halogen:



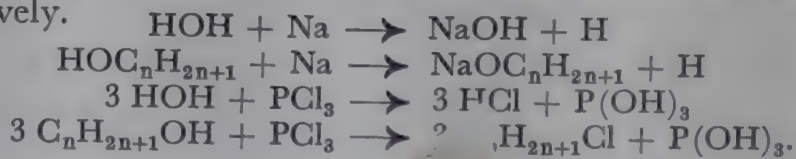
Finally, the synthesis of the alcohols from the alkyl halides and silver hydroxide (moist silver oxide) indicates their constitution, as the halogen atom of the alkyl halide is replaced by the hydroxyl group of the silver hydroxide:



The alcohols thus appear to be hydroxyl derivatives of hydrocarbons. On the other hand they can be related to water, and may be regarded as alkyl derivatives of water:



Indeed some properties of alcohols are characteristic of water, and others are encountered for which the hydrocarbon component is responsible. The reactions between alcohols and sodium or the phosphorus halides are completely analogous to the corresponding reactions between water and sodium or phosphorus compounds respectively.

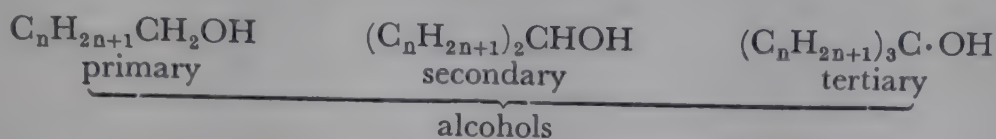


Also, other peculiarities of water, for example its tendency to associate, are found, to a somewhat smaller extent, in the alcohols. In general, the hydrocarbon component of the alcohol lowers the reactivity of the hydroxyl group, so that the latter reacts less vigorously in the alcohols than in water. This effect increases with the size of the alkyl radical. Whilst the lower alcohols (methyl and ethyl alcohols) react readily with sodium, though much less vigorously than water does, the higher alcohols are comparatively inert towards sodium.

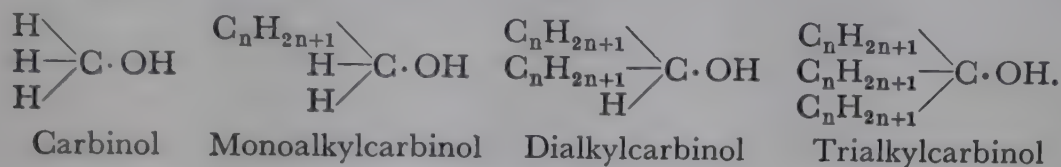
As the alkyl radical increases in size in the alcohol and therefore exerts an increasing effect on the general character of the compound, the character of the hydrocarbon is noticed more and more strongly in the physical and chemical

properties of the alcohol. The lower alcohols, methyl alcohol, and ethyl alcohol are miscible with water in all proportions. The higher homologues are less soluble, and the highest, like the hydrocarbons themselves, are not at all dissolved by water.

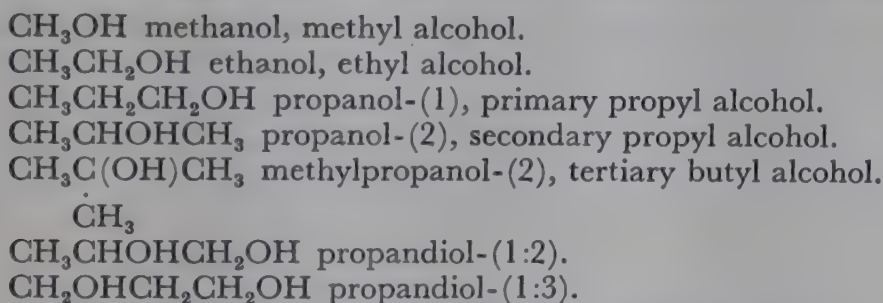
Alcohols are called *primary*, *secondary*, or *tertiary* alcohols according to the position of the hydroxyl group in the molecule. A primary alcohol contains the hydroxyl group attached to a carbon atom which is already linked to two hydrogen atoms. In a secondary alcohol there is only one hydrogen atom attached to the carbon in addition to the hydroxyl group, and in a tertiary alcohol there are no hydrogen atoms linked to the carbon.



The higher alcohols may also be considered as substitution products of the first member of the whole series, *methyl alcohol*, *methanol*, or *carbinol*. The primary alcohols may thus be called monoalkylcarbinols, the secondary, dialkylcarbinols, and the tertiary, trialkylcarbinols.



The Geneva nomenclature prescribes the ending “ol” for a compound which is alcoholic in nature. If the alcohol is polyhydric, the number of OH-groups present is expressed by the endings “diol”, “triol”, etc.; for example:



Occurrence and preparation of the alcohols.¹ Combined with acids as esters the monohydric alcohols are found very widely distributed in the vegetable kingdom. Such esters are contained in many essential oils, and the esters of higher alcohols form the main constituents of the waxes. Methyl and ethyl alcohol are also found in the free state in plants.

The formation of various low alcohols from carbohydrates and proteins by fermentation processes is very important. Methyl alcohol is produced in large amounts by the dry distillation of wood. The lignin of the wood is the substance from which the methyl alcohol originates.

There are numerous methods which are suitable for the preparation of alcohols. Of these, the following will be discussed:

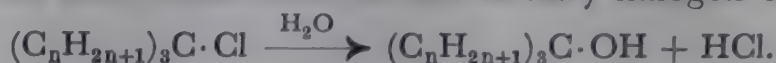
1. Esters are generally decomposed into an alcohol and acid on heating with water, alkalis, or acids. Easily accessible, naturally occurring esters, such

¹ Monograph on the technical syntheses of alcohol, A. RICHARD, *La synthèse industrielle des alcools*, Paris, (1931).

as those occurring in fruits and waxes, can often be used with advantage for the preparation of certain alcohols.

The alkyl halides, esters of the halogen hydracids, have already been dealt with. They too, are good starting substances for the preparation of the alcohols, and are extensively used for this purpose.

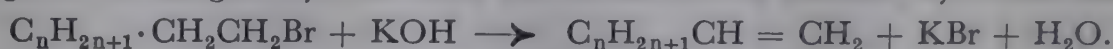
The hydrolytic fission of the alkyl halides with water alone occurs in only a few cases. It has been found with certain tertiary halogen compounds:



It is better to use dilute alkalis, or alkali carbonates, lead oxide, lime-water, or baryta-water, in which case the hydrolysis of the alkyl halide to an alcohol proceeds quite smoothly:



This process, however, is often accompanied by a second which results in the splitting off of halogen hydride and the formation of olefinic hydrocarbons:



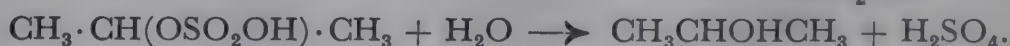
In order to avoid side-reactions of this kind, moist silver oxide is used to hydrolyse the alkyl halide. It reacts even in the cold, or on gentle warming, and usually gives the desired alcohol quite smoothly:



A good method of synthesizing alcohols from alkyl halides, and one that is often used, consists in acting on the latter with silver acetate or sodium acetate, thus converting them first into the acetic esters, and then hydrolysing the latter:



Of the other esters, those of sulphuric acid must be considered in connection with the preparation of alcohols, since the alkyl hydrogen sulphates, as was mentioned in dealing with the olefins, can be easily prepared from the alkylenes and sulphuric acid. Even on boiling with water they break down into the alcohol and sulphuric acid: $\text{CH}_3 \cdot \text{CH} = \text{CH}_2 + \text{HOSO}_2\text{OH} \longrightarrow \text{CH}_3 \cdot \text{CH} \cdot \text{CH}_3$



2. The monoalkyl derivatives of ammonia, called the *primary amines*, break down when warmed with nitrous acid, to give alcohols:



The reaction is often accompanied by side-reactions. Rearrangement of the product may occur, so that instead of the expected primary alcohol, secondary or tertiary alcohols may result. Thus, for example, propylamine gives 42 per cent of propyl alcohol, and 58 per cent of *isopropyl* alcohol. Sometimes the formation of unsaturated hydrocarbons has also been observed.

3. Alcohols can be conveniently prepared by the reduction of aldehydes, ketones, and esters. The reduction of aldehydes always gives primary alcohols, that of ketones, secondary alcohols.



The reducing agents used are sodium amalgam, zinc dust and acetic acid, or zinc and hydrochloric acid. In some cases catalytic reduction with hydrogen and nickel or platinum has been used with good results.

The conversion of an ester of a carboxylic acid into a primary alcohol can be carried out by reduction with sodium and alcohol (Bouveault and Blanc):

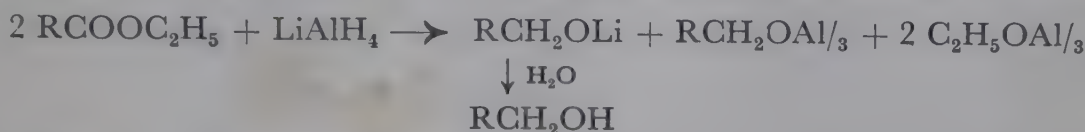


On account of partial hydrolysis of the ester the yield of alcohol is never quantitative. In spite of this the method is useful for the conversion of carboxylic acids into alcohols with the same number of carbon atoms. A modification of the process is the reduction of the acid amides, $C_nH_{2n+1}CO \cdot NH_2$, instead of the ester, but the reaction does not usually proceed so smoothly.

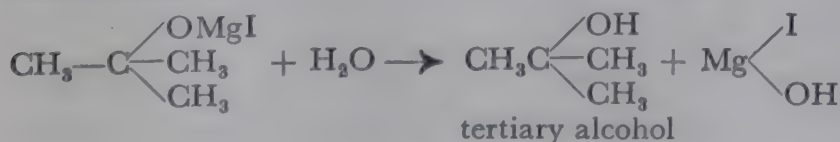
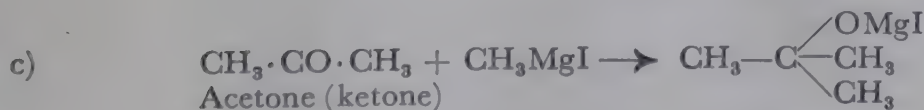
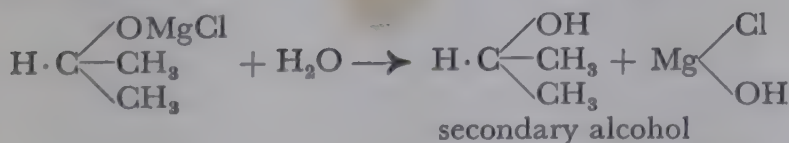
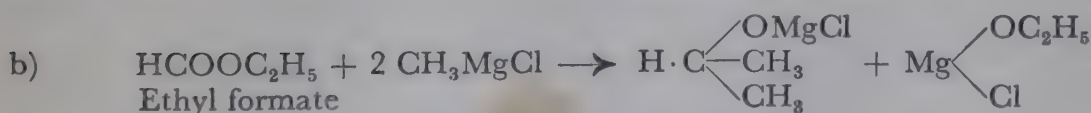
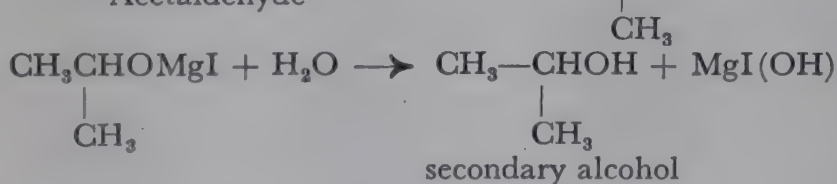
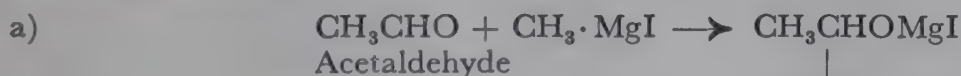
A more modern procedure for the reduction of carboxylic acid esters, due to Finholt, Bond, and Schlesinger, is that carried out with lithium-aluminium hydride $LiAlH_4$, a compound, which can be prepared from lithium hydride and aluminium chloride:

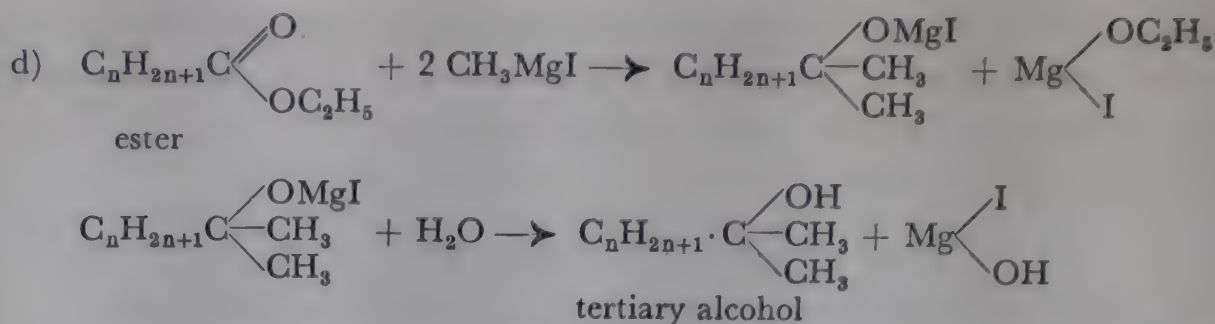


When $LiAlH_4$ acts on a carboxylic acid ester in an indifferent solvent, a smooth reduction to the alcohol often takes place even at room temperature.



4. The reaction of the alkylmagnesium salts (or, in earlier days, zinc dialkyls) with aldehydes, ketones, and esters of carboxylic acids is often used for the preparation of alcohols. Addition products of the alkylmagnesium salts and the substances added are first formed, and these readily break down, when acted upon by water, into alcohols and basic magnesium salts. The aldehydes, and esters of formic acid give secondary alcohols; ketones, and all other esters of carboxylic acids give tertiary alcohols:



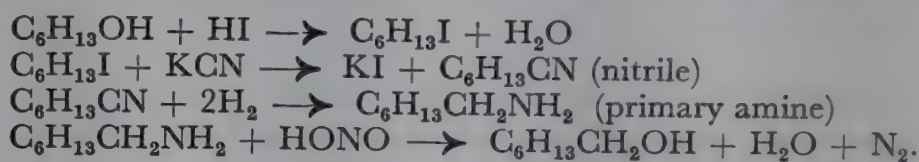


The reaction of the carbonyl compounds mentioned above (ketones, etc.) with alkylmagnesium salts is often preceded by the formation of molecular compounds of the type $\text{R}_2\text{C}=\text{O} \dots \text{Mg}(\text{CH}_3)\text{Br}$, which can be isolated. The latter are converted, according to the nature of the carbonyl compound, either spontaneously or by addition of an excess of alkylmagnesium salt into the stable adducts $\text{R}_2\text{C}(\text{CH}_3)\text{OMgBr}$.

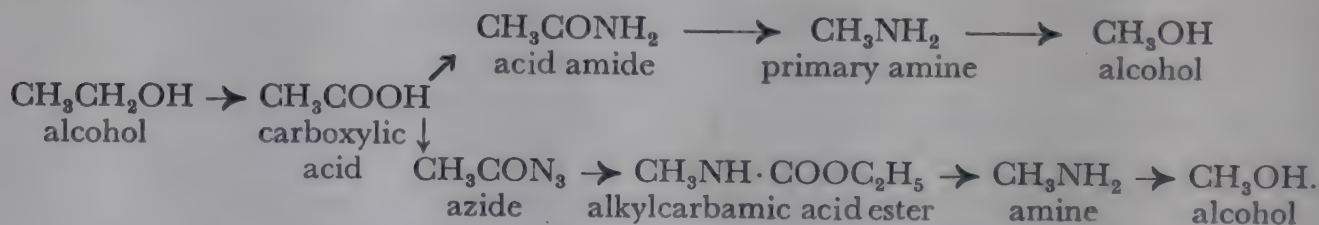
5. P. Schorigin, and A. Morton and I. R. Stevens have found that in place of the Grignard reagents, sodium and organic halogen compounds may often be used fairly satisfactorily for the synthesis of alcohols. These reactions proceed as follows:



By the above practical methods almost any alcohol can be prepared comparatively simply. By a series of consecutive reactions it is also possible to increase the length of the carbon chain in primary alcohols, or to shorten it, i.e. to transform a given alcohol into its higher or lower homologue. The *synthesis* of higher alcohols from lower ones, of which the single steps will be more fully described in other places in this book, can be brought about, for example, in the following way:



The degradation of a higher into a lower alcohol is carried out through the carboxylic acid. The primary alcohol is oxidized to the carboxylic acid, and this is converted into the acid amide, or the acid azide (see p. 226). Methods of *breaking down* both the amide and the azide are known, and will be discussed more fully in the chapter on amines. As the final product of the fairly complicated series of reactions, in both cases the alcohol is obtained:



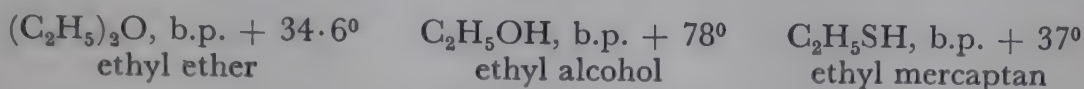
Physical properties of the alcohols. The alcohols are colourless (in thin layers), neutral compounds. The lower members of the homologous series have a burning taste. The solubility in water decreases rapidly with increasing molecular weight. Whilst methyl, ethyl, and propyl alcohols mix with water in all proportions, the next member has only a limited solubility, and the higher members are almost insoluble.

The *boiling points* of the alcohols increase with increasing molecular weight, and the difference in boiling point between two successive members from ethyl alcohol to

decyl alcohol is about 18°–20°. Between two successive higher alcohols it is smaller.

The *melting points* in general increase with increasing molecular weight. Methyl and ethyl alcohols are, however, exceptions, since they melt at a somewhat higher temperature than the third member, propyl alcohol. A similar irregularity is shown in the specific gravity of methanol. It is somewhat higher than that of ethanol, whilst from the second to the ninth member of the series the specific gravity increases by a constant amount. The molecular volumes of the normal primary alcohols also increase from member to member by a constant value.¹

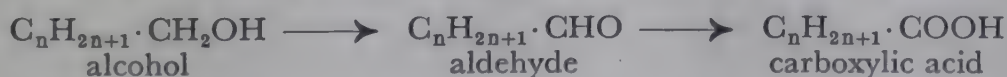
Vapour density determinations at temperatures a little above their boiling points show that the alcohols are associated.¹ This property they share with water, of which they can be regarded as alkyl derivatives. Association is the reason why the alcohols have comparatively high boiling points. Their related compounds, for example, the non-associated ethers, or the little associated thioalcohols (mercaptans) usually boil at lower temperatures, though their molecular weights are higher and the reverse would be expected:



Amongst isomeric alcohols the normal primary alcohols always have the highest boiling point; the secondary and tertiary alcohols boil at lower temperatures. The branching of the carbon chain affects the boiling point in a similar way. On the other hand, the tertiary alcohols often have the highest melting point.

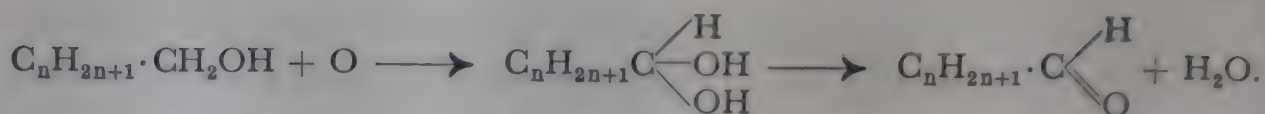
Alcohol		b.p.	m.p.	sp.gr.	} referred to water at 0°. referred to water at 4°.
Methyl alcohol	CH ₃ OH	64.7°	— 97°	0.814	
Ethyl alcohol	C ₂ H ₅ OH	78°	— 114°	0.806	
primary propyl alcohol	C ₃ H ₇ OH	97°	— 127°	0.817	
n- „ butyl alcohol	C ₄ H ₉ OH	117°	— 79.9°	0.823	
n- „ amyl alcohol	C ₅ H ₁₁ OH	137°	—	0.829	
n- „ hexyl alcohol	C ₆ H ₁₃ OH	157°	— 90°	0.833	
n- „ heptyl alcohol	C ₇ H ₁₅ OH	176°	— 35.5°	0.836	
n- „ octyl alcohol	C ₈ H ₁₇ OH	194.5°	— 18°	0.839	
n- „ nonyl alcohol	C ₉ H ₁₉ OH	213°	— 5°	0.842	
n- „ decyl alcohol	C ₁₀ H ₂₁ OH	231°	+ 7°	0.839	} referred to water at 4°.
n- „ undecyl alcohol	C ₁₁ H ₂₃ OH	131° (15mm)	+ 19°	0.833 (23°)	
n- „ dodecyl alcohol	C ₁₂ H ₂₅ OH	143° (15mm)	+ 24°	0.831 (24°)	

General chemical properties of the alcohols. 1. Reactions which are very characteristic and which are useful for distinguishing between primary, secondary, and tertiary alcohols are the oxidation and dehydrogenation of alcohols. *Primary alcohols are oxidized to aldehydes, and the latter to carboxylic acids.*

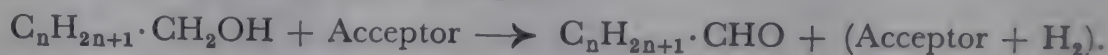


The oxidizing agent always attacks at the carbon atom at which the hydroxyl group is attached. Formerly it was thought that the mechanism of the process could be explained by supposing that first a hydrogen atom of the alcohol was replaced by a hydroxyl group, and then water was split off from the two hydroxyl groups attached to the same carbon atom:

¹ See the table at the end of the book.

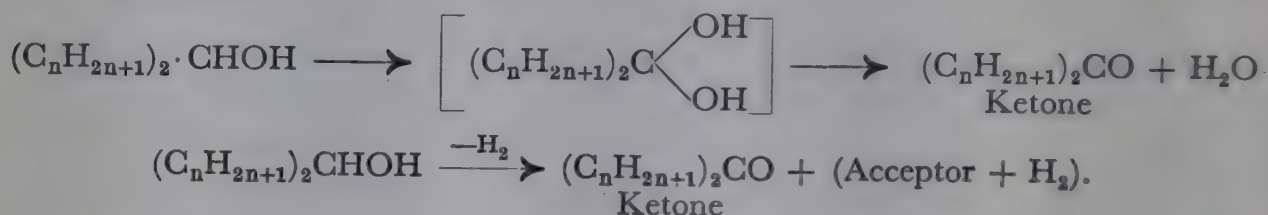


H. Wieland has, however, shown that the formation of aldehydes from alcohols can often take place in the absence of any oxygen, if the substance is treated with a substance which removes hydrogen, e.g. palladium, or Methylene Blue. These withdraw two atoms of hydrogen from the alcohol, and cause its transformation into an aldehyde. It is therefore preferable to speak of “*dehydrogenation*” rather than oxidation in this connection. The substance that removes the hydrogen is called a hydrogen acceptor:



Probably the transition from alcohols to aldehydes can proceed either according to the older view as a true oxidation (hydroxylation), or as a dehydrogenation, according to the choice of experimental conditions and oxidizing agents.

Secondary alcohols give, on oxidation or dehydrogenation, ketones with the same number of carbon atoms:



Tertiary alcohols usually offer greater resistance to oxidation. *When they are attacked, there is a breakdown of the carbon chain and carboxylic acids (or ketones) are formed containing fewer carbon atoms than the original alcohol.*

It is clear that, knowing the products of oxidation of an alcohol, it is possible to decide whether it is a primary, secondary, or tertiary alcohol.

2. As was mentioned in the introduction to this chapter the hydroxyl hydrogen of the alcohols can be replaced by a metal. The *alcoholates* are thus formed: $\text{C}_n\text{H}_{2n+1}\text{OM}^{\text{I}}$.

Of these, the alcoholates of the alkali metals are specially important. They are formed very readily from the metals and lower alcohols, hydrogen being evolved at the same time. Higher alcohols react sluggishly.



After evaporating the excess alcohol, the sodium alcoholate is left as an amorphous powder, which only loses the last molecule of combined alcohol at about 200°. The alcoholates can only be preserved in the absence of water. They are decomposed by water into alcohols and metal hydroxides:



Amongst the numerous other known alcoholates, those of *aluminium* are of interest because they can be distilled *in vacuo* without decomposition.

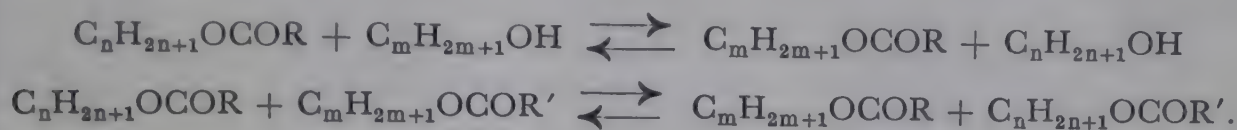
They also possess the remarkable property of adding alcohol (Meerwein), producing complex acids, the so-called alkoxoacids, which are monobasic, and can be titrated quite well:



The alcoholates, especially those of the alkali metals, find many uses in

organic chemistry. They serve as condensing and alkylating agents, and for the introduction of the $C_nH_{2n+1} \cdot O-$ group into other molecules.

3. The esterification of alcohols, of which the mechanism has already been discussed (p. 73) occurs with all inorganic and organic acids and their derivatives (acid halides, anhydrides, etc.). The very important products, the esters, will be dealt with in greater detail in other parts of this book, except the alkyl halides, which have already been discussed. As a general property of the esters it may be mentioned here that according to L. Claisen, Purdie, Bertoni, Haller, Henry, and others, when esters are heated with other alcohols or other esters, double decomposition takes place, the alcohol residues being more or less completely exchanged. The process is called "*transesterification*". It is catalytically accelerated by the presence of small amounts of acid or alkali:



The exchange of alkyl and acid radicals between different esters, can therefore take place in a similar way to the exchange of ions between salts:



The analogy between salts and esters, already manifest in their methods of preparation, is thus extended. This has been taken into account in naming esters, since names like methyl acetate (methyl ester of acetic acid), and ethyl nitrate (ethyl ester of nitric acid) are modelled on those of inorganic salts.

Transesterifications very probably often occur in living plants and animals.

4. The hydroxyl group of alcohols can be directly replaced by the ammonia residue only with difficulty and in poor yield. Merz has carried out such reactions using zinc chloride ammonia at 250°:



Secondary and tertiary amines, $(C_nH_{2n+1})_2NH$ and $(C_nH_{2n+1})_3N$, respectively are formed at the same time.

Methyl alcohol, CH_3OH . In the free state methyl alcohol is rarely found in nature, and then only in traces (e.g. in essential oils). Derivatives of methyl alcohol are, however, more common. Some plant oils contain methyl esters. Oil of wintergreen contains methyl salicylate, $C_6H_4(OH) \cdot COOCH_3$, oil of jasmine contains methyl anthranilate, $C_6H_4(NH_2) \cdot COOCH_3$. Methyl ethers are found in nature very frequently; some natural pigments, alkaloids, etc., belong to this class.

Until recently the sole method of preparing methyl alcohol technically was the destructive distillation of wood. In the liquid distillate, pyroligneous acid, there are acetic acid (10 per cent), acetone (up to 0.5 per cent), acetaldehyde, allyl alcohol, methyl acetate, ammonia, and amines, together with 1.5–3 per cent of methyl alcohol. The acetic acid is separated by distilling into hot milk of lime, thus fixing the acid as calcium acetate. The separation of acetone and methyl alcohol is more difficult as the boiling points are so close (acetone 56.5°; methyl alcohol, 64.8°). In spite of this it is possible, technically, to separate the methyl alcohol almost completely from the substances which accompany it by

careful rectification in fractionating units. Impure methyl alcohol is called "wood spirit".

In more recent times a method has been devised of reducing carbon monoxide to methyl alcohol by hydrogen in the presence of mixtures of metal oxides (zinc and chromium oxides) as catalysts (Bad. Anilin- und Sodafabrik; Patart):



The process requires a high temperature (about 450°) and the application of pressure (for example, 200 atmospheres).

A large part of the demand for methanol is supplied at present by this process. It has superseded to a great extent the older method of making the alcohol from wood. *Isobutyl* alcohol and other substances (e.g. liquid hydrocarbons) are formed as by-products, and by the use of other catalysts (cobalt salts) may be made the chief products of the reaction. Both *isohexyl* alcohol, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)\text{CH}_2\text{OH}$, and *isohexyl* alcohol, $(\text{CH}_3)_2\text{CHCH}_2\text{CH}(\text{CH}_3)\text{CH}_2\text{OH}$, are easily obtained in large quantities if the catalysts are changed.

Chemically pure methyl alcohol is best obtained by hydrolysis of an ester, e.g. the crystalline ester, dimethyl oxalate, $\text{CH}_3\text{OOC} \cdot \text{COOCH}_3$.

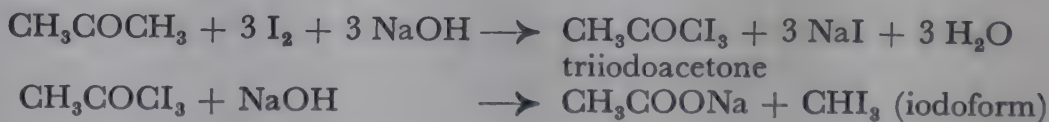
Pure methyl alcohol is a mobile, colourless liquid, which smells quite similar to ethyl alcohol. It burns with a non-luminous, pale blue flame. Methyl alcohol is an intoxicant, and a powerful poison; the drinking of beverages containing it often leads to injuries to the eyes, blindness, and finally death. Its use as a beverage is therefore strictly prohibited.

The oxidation of methyl alcohol gives, in successive stages, formaldehyde, formic acid, and carbonic acid:



Methanol is extensively used in industry. It is used for methylating, e.g. in the production of mono- and dimethylaniline, the preparation of methyl chloride, dimethyl sulphate, and the methyl ester of toluenesulphonic acid, for the production of formaldehyde, for denaturing spirits, as a solvent for lacquers and perfumes.

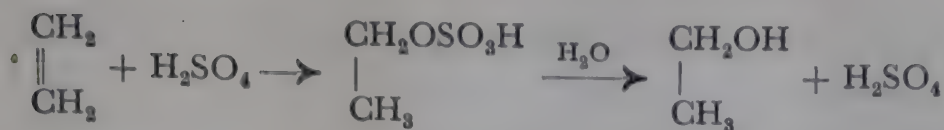
The presence of acetone in methyl alcohol can be detected by the "iodoform test", which depends upon the fact that acetone readily gives iodoform when treated with iodine and alkali:



Iodoform is recognized by its smell, and its quantity can be determined gravimetrically.

Ethyl alcohol, $\text{C}_2\text{H}_5\text{OH}$. Ethyl alcohol is probably formed in nature rather frequently by fermentation of carbohydrates. It can, however, be detected only in small amounts in the soil, in the sea, and in the air. It can also be detected in plants, animal tissues, and in the blood, but only in traces.

Ethyl alcohol can be synthesized by any of the general methods which have already been described as methods of preparing primary alcohols. In the industrial preparation of this important compound, however, only a few processes come into consideration. The preparation of alcohol from ethylene through ethyl hydrogen



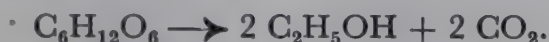
sulphate is too expensive on account of the large amounts of sulphuric acid required, even though ethylene (e.g. from natural gas, or by reduction of acetylene) is cheap enough.

Better results are obtained from the synthesis from acetylene. Water is added on to this unsaturated hydrocarbon by the method described on p. 70, mercury salts being used as catalysts. Acetaldehyde is formed, which is then catalytically reduced to ethyl alcohol by hydrogen in the presence of nickel.

Large quantities of alcohol were made by this method during the Great War 1914/1918, and also later. As far as expense is concerned, however, this method always stands second to those in which ethyl alcohol is made by the fermentation of carbohydrates.

“**Alcoholic fermentation**”¹ is one of the most interesting and, from the economic point of view, one of the most important of chemical processes. In spite of extensive investigation carried out over many decades, all the steps in the process have not even yet been elucidated.

Natural sugars, such as glucose ($\text{C}_6\text{H}_{12}\text{O}_6$) and fructose, which are widely found in fruit juices, decompose into ethyl alcohol and carbonic acid when yeasts grow in their dilute solutions. The reaction proceeds to the extent of 94–95 per cent according to the equation:



This fact was known as far back as the end of the eighteenth century. Pasteur proved later that the yeasts which started the fermentation came from the air, and that sugar solutions which were sterilized, and were kept free from germs, did not ferment. Hence, alcoholic fermentation is associated with yeast. The view that the breakdown of the sugar into alcohol and carbon dioxide was intimately connected with the life-process of the yeast was held for a long time, and yeast was called an *organized ferment*. The contrary views of Liebig, who regarded the decomposition of the sugar as a phenomenon accompanying the growth of the yeasts, but did not consider it to be part of the life-process of the microorganisms themselves, did not find general acceptance. In 1897, Ed. Buchner reported the decisive experiments which elucidated the problem at once. By grinding yeast cells with sand, Buchner destroyed their membranes to a large extent. From the mass of yeast, prepared in this way, a juice was then obtained by application of high pressure. This was free from yeast cells but was still capable of fermenting glucose to give alcohol and carbon dioxide. He also observed that fermentation still occurred even when antiseptics were added which inhibit the life-process of the yeast. It was thus proved that the substance responsible for the alcoholic fermentation was present within the yeast cell, and that it could be separated from the cell and carry on its functions outside it.

The discovery of “*cell-free fermentation*” was of fundamental importance for the interpretation of fermentation processes. The hypothesis of “organized” ferments was shaken and it was proved that a non-living substrate could effect the decomposition of sugars catalytically. This and similar substances, of which only some of

¹ A. HARDEN, *Alcoholic Fermentation*, 4th ed., London, (1932).

the structures have at present been established and which therefore can best be defined by their effects, were called "*unorganized ferments*", or later "*enzymes*".¹ Buchner gave the name *zymase* to the enzyme which brought about the alcoholic fermentation.

Zymase is not affected by antiseptics, such as salicylic acid, toluene, etc. It can be dried without losing its activity. Later investigation has shown that the enzyme system responsible for the alcoholic fermentation is not composed of a single enzyme, but of a whole series of them, amongst which the zymases and carboxylase are of special importance in the following considerations.

Such a complicated process as the decomposition of glucose into two molecules of ethyl alcohol and two molecules of carbon dioxide must necessarily take place through a number of intermediate steps. By devising special experimental conditions, attempts have been made to stop the reaction at different stages, and thus establish the mechanism of alcoholic fermentation.

According to most recent views (Grüss, and particularly Willstätter) the sugar is not fermented directly but is first converted by specific enzymes into *glycogen* (see p. 359), from which subsequently the forms of sugar capable of fermentation arise. Other investigators hold the view that glucose is not converted into glycogen, but that first glucose-1-phosphate is formed from it, which then rearranges to glucose-6-phosphate.

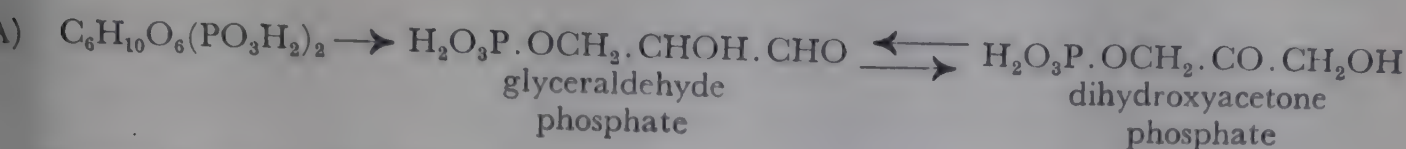
In the succeeding stage of the fermentation process, the so-called "pre-fermentation", the "zymophosphate" discovered by Harden and Young certainly plays an important part, which has only recently been generally recognized. This Harden-Young ester has the structure of fructofuranose-1 : 6-diphosphate (for nomenclature, see chapter on carbohydrates). In addition, two other phosphoric acid esters are present in small amounts, the so-called Robison ester (glucopyranose-6-phosphate) and mannose-6-phosphate. By partial hydrolysis of the Harden-Young ester, the Neuberg ester (fructofuranose-6-phosphate) can be formed.

Whilst formerly the view was held that the glucose molecule, or its phosphorylated form, was first broken down during fermentation into two molecules of methylglyoxal, the important investigations of Embden in 1933, and subsequently those of Meyerhof, Nilsson, and others, gave a new insight into the reaction mechanism. O. Warburg and co-workers, have recently developed an interpretation of the fermentation mechanism, based on new experimental evidence which differs somewhat from that of Meyerhof. Which of these views will finally supersede the other cannot at present be decided. In the following paragraphs an attempt is made to present, in a somewhat simplified manner, the reaction steps which appear to be best established by experimental evidence.

The first phase of fermentation consists in the transformation of hexose diphosphate into two molecules of *triose phosphates*, viz. *dihydroxyacetone phosphate* and *glyceraldehyde phosphate*. This reaction takes place under the influence of an

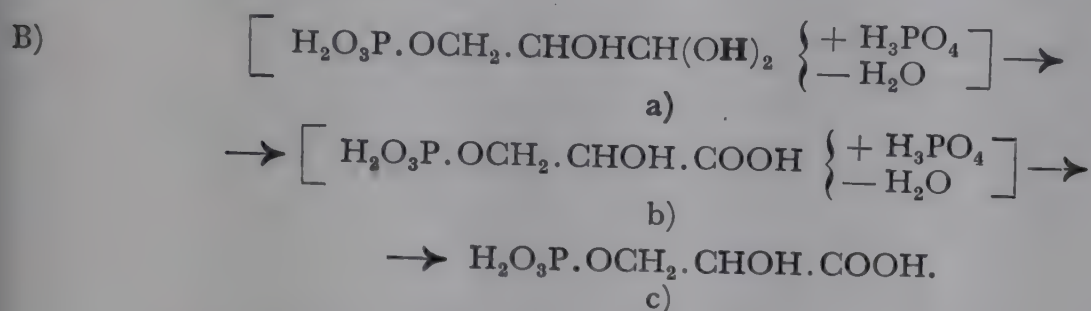
¹ On enzymes see K. G. FALK, *The Chemistry of Enzyme reactions*, 2nd ed. New York, (1924). — H. v. EULER, *Chemie der Enzyme*, Munich, (1925-34). — C. OPPENHEIMER, *Die Fermente und ihre Wirkungen*, Leipzig, (1924-29). — R. WILLSTÄTTER, *Untersuchungen über Enzyme*, Berlin, (1928). — E. WALDSCHMIDT-LEITZ and R. P. WALTON, *Enzyme actions and properties*, New York, (1929). — *Ergebnisse der Enzymforschung*, vol. 1-6 (1932-1938) edited by F. F. NORD and R. WEIDENHAGEN. Leipzig. — HENRY TAUBER, *Enzyme Chemistry*, London, (1937). — F. F. NORD and R. WEIDENHAGEN, *Handbuch der Enzymologie*, Leipzig, (1940). — E. BAMANN and K. MYRBÄCK, *Die Methoden der Fermentforschung*, Leipzig, (1941). — JAMES B. SUMMER and G. FRED SOMERS, *Chemistry and Methods of Enzymes*, New York, (1943).

enzyme "hexokinase" (also known as "aldolase") which can be isolated in a crystalline form.

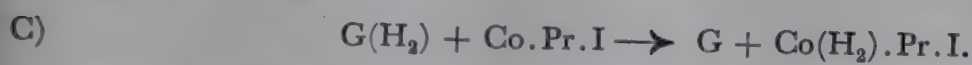


Glyceraldehyde phosphate and dihydroxyacetone phosphate form a reversible equilibrium, which is established under the influence of an enzyme "isomerase" and is shifted in favour of the former according as glyceraldehyde phosphate is removed from the equilibrium by further transformations.

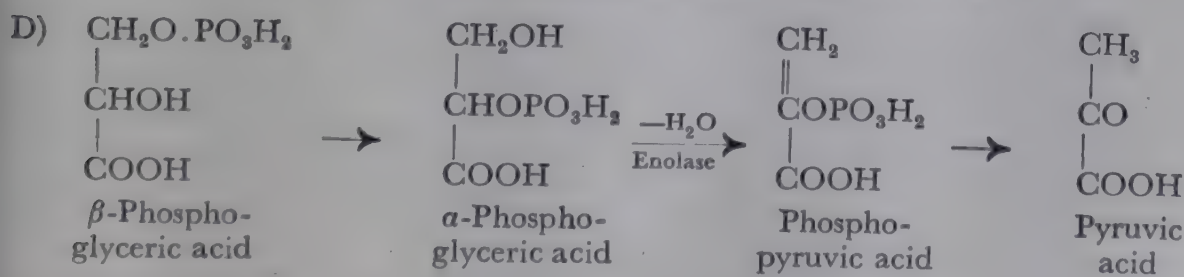
The next step is the further oxidation of glyceraldehyde phosphate by the action of a specific enzyme, whose coenzyme principle (prosthetic group) is cozymase (Co) and whose protein component (Pr. I) has been isolated by Warburg in a crystalline form. It is not, however, the glyceraldehyde phosphate itself which undergoes oxidation, but an intermediate, unstable glyceraldehyde diphosphate (a) whose constitution is not yet completely elucidated (probably glyceraldehyde-1:3-diphosphate). The oxidation product is glyceric acid diphosphate (b), which subsequently loses one molecule H_3PO_4 to give *phosphoglyceric acid* (= glyceric acid phosphate) (c):



In this dehydrogenation process the cozymase group (Co) of the oxidizing enzyme (Co·Pr.I) takes up the two H-atoms (printed in heavy type in formula (a)) of the hydrated form of glyceraldehyde diphosphate (indicated by $G(H_2)$ in the following equation), and is thus transformed into dihydrocozymase ($Co(H_2)$):



The β -phosphoglyceric acid formed according to equation B is first converted into α -phosphoglyceric acid, and then, by the enzyme *enolase* (which has been isolated in a crystalline form) into phosphopyruvic acid, which by hydrolysis gives *pyruvic acid* (equation D). Pyruvic acid has long been known to be an intermediate product in the fermentation process, through the work of Neuberg, and has been isolated from fermentation liquor. Pyruvic acid is decomposed by an enzyme *carboxylase* into *carbon dioxide* and *acetaldehyde* (equation E):



The acetaldehyde obtained according to equation E is finally reduced to ethyl alcohol (equation F). The two H-atoms required for this reduction are provided by the dihydrocozymase, formed according to equation C, which is thus reconverted into cozymase, and the latter is now available for a further dehydrogenation according to equation C.



According to the investigations of Negelein and Warburg, the protein Pr.II, which is combined with the hydrogenated cozymase in the reaction F, differs from the protein which takes part in the oxidation reaction in equation C (Pr.I). The cozymase and its reduced form thus combine alternately with protein I (to form the oxidizing, or dehydrogenating, enzyme) and with protein II (to form the reducing enzyme).

The constitution of the effective group of cozymase is now known, and the above equations can therefore to a large extent be represented by structural formulæ. This will be dealt with in the chapter on vitamins. The equations presented here serve to show first of all, how the reaction mechanism of the alcoholic fermentation is governed by the cooperation of numerous enzymes.

Recently, the constitution of *cocarcboxylase*, the coenzyme-active principle of the carboxylase necessary for the fermentation (equation E), has also been established. It is a pyrophosphoric acid ester of vitamin B₁, thiamine pyrophosphate, which is described in the chapter on vitamins.

The fermentation scheme outlined above offers a satisfactory explanation of the fact, that under normal conditions of fermentation ethyl alcohol and carbon dioxide are formed in approximately equimolecular quantities (2 molecules each from 1 molecule of glucose). It also takes into account, that there is always some glycerol (about 3 per cent) formed as a by-product. This may be formed by the reduction of either dihydroxyacetone phosphate or glyceraldehyde phosphate with subsequent splitting off of the phosphoric acid residue; here also, the reduced cozymase may act as the hydrogen donor. The quantity of glycerol can be increased, as was first shown by Neuberg, Connstein, and Lüdecke, by adding bisulphites (or Na₂SO₃, which is converted by CO₂ into the bisulphite) to the fermenting liquid, which combine with the acetaldehyde and prevent it from being further acted upon. As a result of its elimination shortly before the final stage of the fermentation process, the active hydrogen, which would normally be used in reducing it, is transferred to a triose molecule (i.e. triose phosphate or dephosphorylated triose, dihydroxyacetone or glyceraldehyde) and reduces it to glycerol:



Our knowledge of the fermentation mechanism, as outlined above, has been gained chiefly by the technique of employing cell-free extracts from yeast as the source of enzymes, i.e. with the unorganized zymase system. It has not yet been proved whether in living yeast the processes take place in exactly the same way.

The phosphorylating reactions accompanying the sugar degradation have also been extensively investigated. Parnas holds the view that the first phosphate donor for the phosphorylation of glucose, or of the hexose monophosphate formed from glycogen and free phosphate, is *adenosine triphosphate*, which is thus converted into adenylic acid, poorer in phosphorus (see nucleic acids, Ch. 62.) This reaction probably takes place in two stages via adenosine diphosphate as intermediate product, which can be isolated under suitable conditions. The adenylic acid formed from adenosine triphosphate by loss of H₃PO₄ is rephosphoryla-

ted to adenosine triphosphate, in the first phase of fermentation by creatine phosphate (see p. 295), and later by the phosphorylated fission products of the sugar, particularly by phosphopyruvic acid. In the stationary phase of the fermentation the transfer of the phosphoric acid residue from adenosine triphosphate to glucose is assumed to take place directly, without previous splitting off of H_3PO_4 (transesterification, see p. 87). It must be assumed that these processes of transesterification also occur under the influence of specific enzymes.

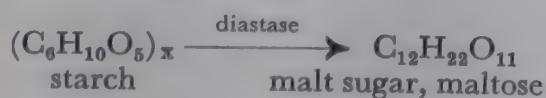
In order that the fermentation of sugar should proceed smoothly it is necessary to choose the most favourable conditions for the growth of the yeast (*Saccharomyces*). The optimum temperature lies between 30° and 37° . Below 5° and over 50° the fermenting power of yeast is completely inhibited. Too high a concentration of sugar in the solution is detrimental to the yeast. A sugar content greater than 12–15 per cent can seldom be endured. In addition, the alcohol produced in the fermentation hinders the growth of the yeast, and stops it altogether if the concentration becomes too high. The various species of yeast are different as regards their sensitivity in this direction. There is wine yeast which can produce up to 20 per cent alcohol, but in the majority of cases the fermentation is completely stopped at concentrations less than this. Finally, it is necessary for the growth of the yeast to add nutritional salts, particularly potassium and magnesium salts, and salts of phosphoric acid, and above all, nitrogen compounds, which are necessary for the building up of the characteristic protein of the yeast. Amides and amino-acids are specially suitable as sources of nitrogen, but inorganic ammonium salts also answer the purpose.

The number of species of yeast known is great. Among them are those which live on the surface of the fermenting liquid (*top yeast*) and others which collect on the bottom of the vessel (*bottom yeast*).

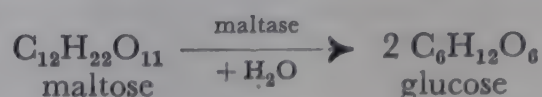
The most important by-products of alcoholic fermentation are acetaldehyde, acetal, glycerol, succinic acid, and *fusel oil*, a mixture of butyl and amyl alcohols and higher homologues. Succinic acid and fusel oil do not arise from the sugar, but owe their origin to a special fermentation of amino-acids which are formed from the protein of the feeding substrate of the yeast and from the protein of the yeast cells and which are continually being reformed by the yeast cells on account of the metabolism of the latter.

For the technical preparation of ethyl alcohol the naturally occurring simple sugars would be too expensive and their quantity too small. The cheaper polysaccharides, especially starch, and, more rarely, hydrolysed cellulose, are used, and are converted into the more simple fermentable carbohydrates by fermentation processes.

The most important raw materials containing starch are potatoes, and the various kinds of grain, including maize and rice. The potatoes are first heated under pressure in closed boilers, thus breaking down the cell walls and bursting the starch grains. The disintegrated mass is put into a mash-tun and malt is added. Malt is germinating barley, which contains a large quantity of a starch-hydrolysing enzyme, *diastase*, which is widely distributed in the vegetable kingdom. The starch is hydrolysed by the action of the diastase. It takes up water and breaks down into a disaccharide, malt sugar (maltose).



When the conversion into sugar has gone far enough, some pure-culture brewer's yeast is added to the liquid. It rapidly grows in the sugar solution. The yeasts contain a ferment, called *maltase*, which breaks down the malt sugar further into glucose:



At this stage of the decomposition, those enzymes in the yeast, to which the collective name zymase has already been given, set to work and ferment the glucose giving alcohol and carbon dioxide.

The fermented mash is now fractionally distilled, thus separating, as far as possible, the ethyl alcohol from the other products of fermentation, and water. Since the boiling points of ethyl alcohol and water are not widely different, to obtain fractions rich in alcohol it is necessary to use apparatus in which the condensation of the distillate and its re-distillation are repeated many times. By the use of fractionating columns and dephlegmators, i.e. apparatus (attached to the distillation vessel) on the cool walls of which part of the vapour is re-condensed, it is possible to distil over from the fermented liquid, a crude spirit containing a fairly high percentage (up to and over 90) of alcohol. The residue, which remains in the distilling vessel, and contains, in addition to water, all the non-volatile substances (mineral salts, proteins, fats, glycerol, succinic acid) is a valuable fodder for cattle. It is called wash.

To purify the crude spirit further it is fractionally distilled. The first fractions contain the easily volatile acetaldehyde and acetals. The main fraction consists of 90–95 per cent alcohol. In the final fractions, the “fusel alcohols”, chiefly two amyl alcohols, and also *isobutyl* and some *n*-propyl alcohol are found. They are all produced by the fermentation of amino-acids. Fusel oil contains in addition small quantities of higher alcohols and fatty acids and their esters, and furfural.

Pure “absolute” alcohol boils at 78.3°, but cannot be obtained by simple distillation, since a mixture of 95.5 per cent alcohol and 4.5 per cent water forms a constant-boiling mixture. In order to remove the last 4 per cent of water, it is boiled with quicklime. The water is removed by the lime and pure alcohol distils over.

A newer method for removing water from alcohol depends on the addition of benzene to the 95 per cent alcohol, and then distilling. At first a ternary mixture (alcohol + water + benzene) distils over at 64.85°, then a binary mixture consisting of benzene and alcohol at 68.25°, and finally pure alcohol at 78.3°.

The presence of a small amount of water in ethyl alcohol can be detected by adding a solution of ethyl formate and anhydrous sodium ethylate in absolute alcohol. The smallest amount of water present hydrolyses the ethyl formate, and sodium formate, which is very difficultly soluble in alcohol, is precipitated.

Absolute ethyl alcohol is a clear liquid which burns with a blue flame and has a characteristic odour. Its specific gravity is 0.793 (at 15°). It is miscible with water in all proportions, the mixing being accompanied by a contraction (from 52 volumes of alcohol and 48 volumes of water, 96.3 volumes of dilute alcohol are formed). The percentage of alcohol in a dilute alcohol is most easily found by determining the specific gravity. The “alcoholometer” is a hydrometer so calibrated that it reads the alcohol content directly, in per cent by weight or volume.

The most certain method of detecting ethyl alcohol analytically is to prepare its

benzoic ester, $\text{C}_6\text{H}_5\text{COOC}_2\text{H}_5$ or its *p*-nitrobenzoic ester, $\text{O}_2\text{N}\cdot\text{C}_6\text{H}_4\text{COOC}_2\text{H}_5$. These are obtained by shaking benzoyl chloride or *p*-nitrobenzoyl chloride with the aqueous liquid containing alcohol, and sodium hydroxide solution. The esters produced can be extracted from the alkaline liquid with ether. Ethyl benzoate has a characteristic smell, and ethyl *p*-nitrobenzoate melts at 57° . Both reactions are very sensitive.

Ethyl alcohol is used extensively in the laboratory and in industry as a solvent and extracting agent, as a fuel, as the starting point in the preparation of pharmaceutical products and perfumes, for the preparation of acetic acid, lacquers, varnishes, dyes, certain artificial silks, etc. The largest amounts of ethyl alcohol are, however, consumed by human beings, partly in the form of liqueurs, which are made artificially from pure alcohol, water, sugar, and essences, and partly in the form of alcoholic drinks, which are made from raw materials containing starch or sugars, by various processes of fermentation. Subsequent distillation is often carried out to convert this latter type into the more strongly alcoholic "spirits".

The following table gives some of the more common alcoholic beverages arranged according to their origin and method of preparation.

Alcoholic drinks have been known since ancient times and are made and used by many races who even yet stand at a very low level of civilization. They make them from natural substances containing sugar and starch. Ethyl alcohol in small doses stimulates

Raw material	Alcoholic beverage	
	without distillation	with distillation
(a) Substances containing sugar:		
1. Grapes	Wine	Brandy
2. Fruit	Cider, Perry	
3. Currants	Currant wine	
4. Molasses		Rum, arrack
5. Cherries		Cherry brandy
6. Plums	Plum wine (China)	Slivovic
7. Juniper berries		Hollands
8. Residues from wine and cider manufacture		Weak spirits
(b) Substances containing starch:		
1. Barley	Beer	Corn brandy
2. Wheat	Beer	Corn brandy
3. Rye	Beer	Corn brandy, Whisky
4. Potatoes		Brandy
5. Maize		Whisky
6. Rice	Saki (rice beer)	Arrack

the human organism, but the effect soon passes into narcosis and slackening. In larger doses it is a poison. It is to a great extent used up by the organism, but at the same time exerts an injurious effect, which can lead, in the case of chronic alcoholism to degeneration of various organs.

Propyl alcohols, $\text{C}_3\text{H}_7\text{OH}$. There are two structurally isomeric propyl alcohols, a primary and a secondary:

$\text{CH}_3\text{CH}_2\text{CH}_2\text{OH}$
primary propyl alcohol
(propanol-1)

$\text{CH}_3\text{CHOHCH}_3$
secondary propyl alcohol
(isopropyl alcohol, propanol-2).

PRIMARY PROPYL ALCOHOL is found in the tail fraction of the distillate from the alcoholic fermentation. ISOPROPYL ALCOHOL is easily obtained by reduction of acetone. In America it is now manufactured on a large scale from the cheaply available propylene,

which is obtained from cracking gases of the petroleum refineries by absorption in sulphuric acid and hydrolysis of the ester formed. It often replaces ethyl alcohol for industrial purposes; moreover, large quantities are used in the manufacture of acetone.

Both propyl alcohols are more poisonous and are more strongly intoxicating than ethyl alcohol. Their use in beverages is prohibited.

Butyl alcohols, C_4H_9OH . The four possible structurally isomeric butyl alcohols are known:

$CH_3CH_2CH_2CH_2OH$	Butanol-1. (Primary) normal butyl alcohol,	b.p. 117°
$CH_3CH_2CHOHCH_3$	Butanol-2. Secondary butyl alcohol,	b.p. 100°
CH_3CHCH_2OH	Methyl-propanol-1. (Primary) <i>isobutyl</i> alcohol,	b.p. 108°
$\begin{array}{c} \\ CH_3 \\ CH_3C(OH)CH_3 \\ \\ CH_3 \end{array}$	Methyl-propanol-2. Tertiary butyl alcohol,	b.p. 83° .

NORMAL, PRIMARY BUTYL ALCOHOL is found to the extent of 6–8 per cent in the liquid obtained by fermenting glycerol or mannitol by *B. butylicum*. It is made on a large scale from starch, and starchy substances by fermentation with *B. acetobutylicus*. The product contains about 60 per cent butyl alcohol, 30 per cent acetone and 10 per cent ethyl alcohol. Butyl alcohol is a useful article of commerce, as it is an excellent solvent for nitrocellulose lacquers.

SECONDARY BUTYL ALCOHOL is prepared by the reduction of methyl ethyl ketone:



or recently from the normal butylenes, supplied by the mineral oil industry, via the acid sulphuric acid ester.

PRIMARY ISOBUTYL ALCOHOL is a constituent of fusel oil, from which it can be obtained by fractional distillation. It owes its formation to the fermentation of a protein amino-acid, valine:



The esters of *isobutyl* alcohol with *isobutyric* acid and angelic acid are contained in Roman camomile oil. The free alcohol is also present in the oil from the distillation of wood. It is manufactured industrially from water gas ($CO + H_2$) with cobalt salts as catalyst. It is used in perfumery, in the production of fruit esters (butyl acetate) and artificial musk, as a solvent in the lacquer industry, and for the synthesis of pharmaceutical products.

TERTIARY BUTYL ALCOHOL is the only one of the butyl alcohols which is solid at ordinary temperatures (m.p. 25.4°). It is prepared from the methylpropene (*isobutylene*) of the mineral oil industry, and from acetone and methyl-magnesium salts (Grignard):



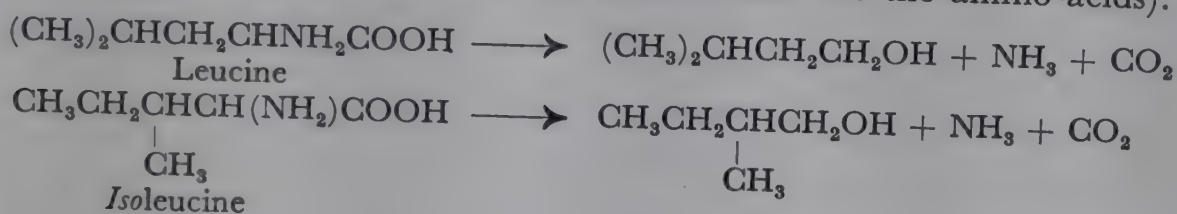
Amyl alcohols, $C_5H_{11}OH$. All eight of the theoretically possible amyl alcohols are known:



b.p. 138°

2. $\text{CH}_3\text{CH}_2\text{CH}_2\text{CHOHCH}_3$	Pentanol-2	b.p. 119°
3. $\text{CH}_3\text{CH}_2\text{CHOHCH}_2\text{CH}_3$	Pentanol-3	b.p. 117°
4. $\begin{array}{c} \text{CH}_3\text{OHCHCH}_2\text{CH}_3 \\ \\ \text{CH}_3 \end{array}$	2-Methylbutanol-1 (optically active fermentation amyl alcohol)	b.p. 128°
5. $\begin{array}{c} \text{CH}_3\text{C}(\text{OH})\text{CH}_2\text{CH}_3 \\ \\ \text{CH}_3 \end{array}$	2-Methylbutanol-2 (amylene hydrate)	b.p. 102°
6. $\begin{array}{c} \text{CH}_3\text{CHCHOHCH}_3 \\ \\ \text{CH}_3 \end{array}$	2-Methylbutanol-3 (3-methylbutanol-2)	b.p. 112.5°
7. $\begin{array}{c} \text{CH}_3\text{CHCH}_2\text{CH}_2\text{OH} \\ \\ \text{CH}_3 \end{array}$	2-Methylbutanol-4 (3-methylbutanol) (optically inactive fermentation amyl alcohol)	b.p. 130°
8. $\text{CH}_3\text{C}(\text{CH}_3)_2\text{CH}_2\text{OH}$	Dimethylpropanol	b.p. 113°

Of these amyl alcohols, the compounds 4 and 7, *optically active* and *optically inactive fermentation amyl alcohol*, are found in fusel oil obtained by alcoholic fermentation, and are, in fact, its chief constituents. The inactive alcohol predominates. Their parent substances are not sugars, but protein amino-acids from which they are produced by a special fermentation (Felix Ehrlich). Inactive fermentation amyl alcohol arises from leucine, the active alcohol from *isoleucine* (for the mechanism of this amino-acid fermentation see the amino-acids).

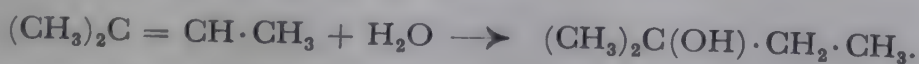


NORMAL PRIMARY AMYL ALCOHOL has also recently been proved to be present in fusel oil. It is formed very probably from another amino-acid, norleucine (see p. 277) by an analogous process.

Crude fermentation amyl alcohol (i.e. the mixture of 2-methylbutanol-4 with a little 2-methylbutanol-1) finds many applications in industry. It is used in making scents, and for the synthesis of fruit esters, i.e. esters with pronounced odours which recall the aroma of certain fruits (amyl acetate, amyl butyrate, amyl valerate); amyl acetate is used in the preparation of nitrocellulose lacquers (varnishes) and in medicine for the treatment of asthma, because of its dilating effect on the blood vessels. Amyl alcohol and sodium is a much used reducing agent, which has certain advantages over a mixture of ethyl alcohol and sodium on account of its higher boiling point.

Amyl alcohol is a more powerful intoxicant, and is more poisonous than ethyl alcohol.

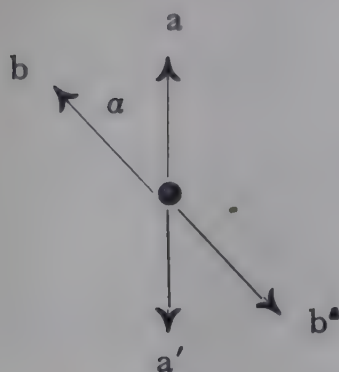
TERTIARY AMYL ALCOHOL, amylene hydrate, (2-methylbutanol-2; m.p.—12°) is used in medicine as a hypnotic. It is prepared from amylene, to which water is added through the agency of sulphuric acid:



Amylene itself, together with isomerides, is formed by the dehydration of fusel oil.

In the optically active fermentation amyl alcohol, we have encountered an

“optically active” substance for the first time. We will now explain more fully the phenomenon of **optical activity**¹ which is of fundamental importance for organic chemistry.



By optically active compounds is understood those which have the power of rotating the plane of vibration of polarized light (i.e. light in which the vibrations are in one plane only) through a certain angle. If, for example, the polarized ray has its vibrations in the direction aa' before entering the optically active substance, the direction on leaving will be bb' , the plane having been rotated through the angle α .

The extent of the rotation depends on the nature of the optically active substance, the solvent, and the wave-length of the light used. It increases with the thickness of the substance through which the polarized light passes, and with the concentration of the solution.² It is also dependent to some extent on temperature.

If α is the angle of rotation, p the number of grams of the optically active substance in 100 grams of the solution, d the specific gravity of the solution, and l the length of the substance through which the light passes, in decimetres, then the angle of rotation for 1 g of the active substance in 1 cm³ of solution and a length of 1 dm., the so-called *specific rotation*, is given by the equation

$$[\alpha] = \frac{\alpha \cdot 100}{l \cdot d \cdot p}$$

The specific rotation is usually given for the sodium light (D-line), and at a definite temperature, say 20°, and is then designated by $[\alpha]_{\text{D}}^{20}$.

Chemical compounds which show the peculiarity of rotating the plane of polarized light fall into two classes. The one comprises only a few inorganic substances, such as quartz, potassium chlorate, potassium bromate, sodium periodate, etc. They all have the common property that the optical activity is closely connected with the crystalline structure, and disappears when the substances are dissolved in liquids, thereby becoming molecularly dispersed. In this case, the capacity of rotating the plane of polarization of light is not due to any special structure of the molecule, but of the crystal, and the investigation of this problem belongs to crystallography. In addition, some organic substances are known, such as benzil which possess optical activity only in the crystalline form.

A second, and extraordinarily large class of organic and inorganic optically active substances behaves differently. These compounds retain their activity even when they are dissolved, and thus broken down into their molecules, or when they

¹ See L. PASTEUR, *Recherches sur la dissymétrie moléculaire des produits organiques naturels*; publ. in *Leçons de chimie professées en 1860 par MM. Pasteur, Cahours, Wurtz, Berthelot, Sainte-Claire Deville, Barral et Dumas*, Paris, (1861). — LANDOLT, *Das optische Drehungsvermögen organischer Substanzen*, 2nd ed. Brunswick, (1898). — A. WERNER, *Lehrbuch der Stereochemie*, Jena, (1904). — A. W. STEWART, *Stereochemistry*, Longmans, Green & Co., (1919). — GEORG WITTIG, *Stereochemie*, Leipzig, (1930). — FREUDENBERG, *Stereochemie*, Vienna, (1933). — ALEXANDER L. WINCHELL, *The Optical Properties of Organic Compounds*, Madison Visc., (1943).

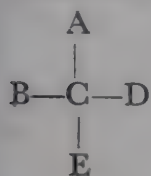
² There are some substances for which this does not hold; they are said to show anomalous rotation.

are investigated in the gaseous state. The power of rotating the plane of polarization of light must, in these cases, be due to a special structure of the molecule, the investigation of which falls within the scope of chemistry. When in the following, optically active substances are referred to, it must be understood that it is substances of the second class which are meant.

To every optically active compound there exists another which has the same chemical and physical properties, but which differs from the first in rotating the plane of polarization by the same amount in the opposite direction. Thus, there is a mandelic acid with a specific rotation of -157° , and another with a specific rotation of $+157^\circ$; or a lævorotatory amyl alcohol $(C_2H_5)CH \cdot CH_2OH$, with the specific rotation -5.9° , and a dextrorotatory isomeride. CH_3

Two such isomerides, which differ neither in chemical nor in general physical properties, but which rotate the plane of polarization of light by the same amount, one to the right, the other to the left, are called *antipodes*, or *enantiomorphic* forms. The dextrorotatory compound is referred to as the *d*-form, and the lævo as the *l*-form.

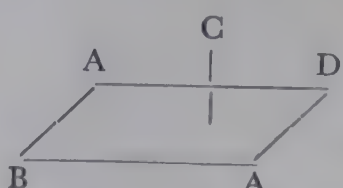
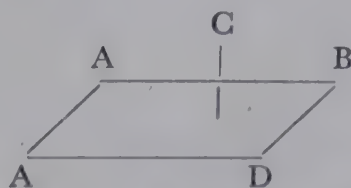
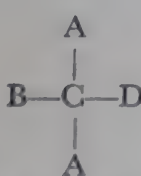
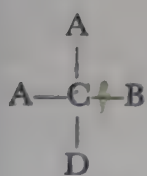
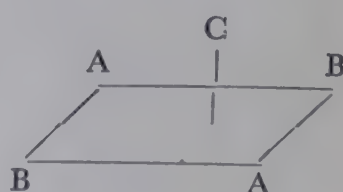
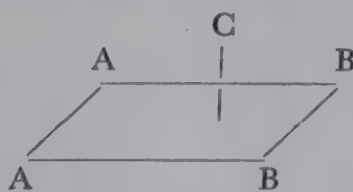
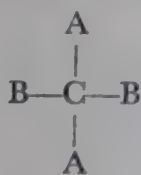
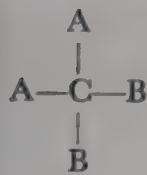
Independently of each other, Le Bel and van 't Hoff in 1874 came to the conclusion that this optical isomerism depended on a different space arrangement of the molecules of the two antipodes. They introduced into chemistry the fundamental concept of the tetrahedral symmetry of the carbon atom. With the simple assumption of the tetrahedral arrangement of the substituents linked to the carbon atom, the existence of two isomeric forms of optically active compounds could be easily explained, and optical activity could be predicted from molecular structure.



Experience shows that only those carbon compounds are optically active which contain at least one carbon atom of which the valencies are saturated by different atoms or radicals. Such carbon atoms are said to be *asymmetric*.

There are two ways of arranging four substituents about a central atom. Either they all lie in one plane, or only three of them do.

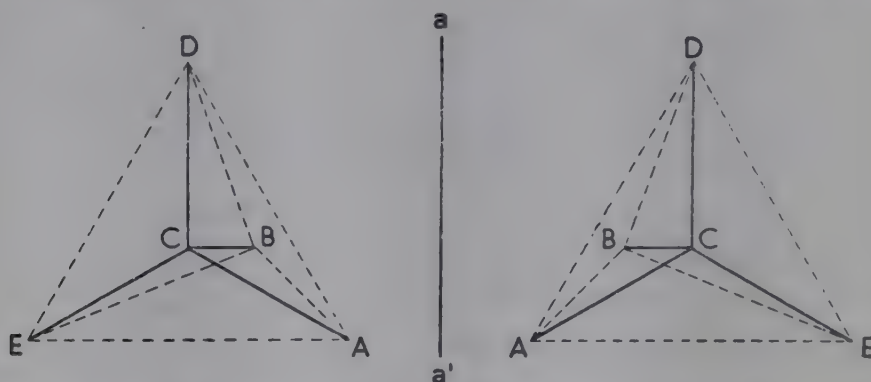
Up to the present, compounds of the formulæ CA_4 , CA_3B , CA_2B_2 , CA_2BD have never been observed to exist in enantiomorphic forms or any other isomeric forms. van 't Hoff and Le Bel therefore drew the conclusion that the four substituents attached to the carbon atom cannot lie in one plane; for if they did, and the carbon atom itself lay inside the plane, or out of it, substances of the type CA_2B_2 and CA_2BD must exist in two stereoisomeric forms:



Le Bel, and particularly van 't Hoff, therefore made the assumption that the

four groups linked to a carbon atom do not lie in one plane. If the positions of the substituents are symmetrical in space, the arrangement must be that of a *regular* tetrahedron, i.e. the four substituents are placed at the apices of a regular tetrahedron, the carbon atom being at its centre. If the arrangement is unsymmetrical, the substituents lie at the apices of an irregular tetrahedron.¹

It is easily seen from a model that this arrangement leads to only one form for substances of the formulæ CA_2B_2 and CA_2BD . On the other hand, those substances which have an asymmetric carbon atom, $A \cdot \overset{\overset{B}{\mid}}{\underset{\underset{E}{\mid}}{C}} \cdot D$, can exist, on a tetrahedral arrangement, in two isomeric forms, which are mirror images of each other.



The theory of Le Bel and van 't Hoff has proved very fruitful for chemical investigation. All phenomena connected with optical activity have been completely and incontestably explained on the basis of this hypothesis.

The tetrahedral structure of simple carbon compounds has recently been confirmed by X-ray diffraction measurements. For example, Debye has shown that carbon tetrachloride has this structure. The distance between two chlorine atoms in carbon tetrachloride is 2.86 Å. On passing from carbon tetrachloride, CCl_4 , to chloroform, $CHCl_3$, and methylene dichloride, CH_2Cl_2 , the distance between two chlorine atoms does not remain constant, but becomes greater (in chloroform it is about 3.5 per cent greater than in carbon tetrachloride). The regular tetrahedron is thus replaced by an irregular one with the valency angle of $112^\circ (\pm 2^\circ)$.

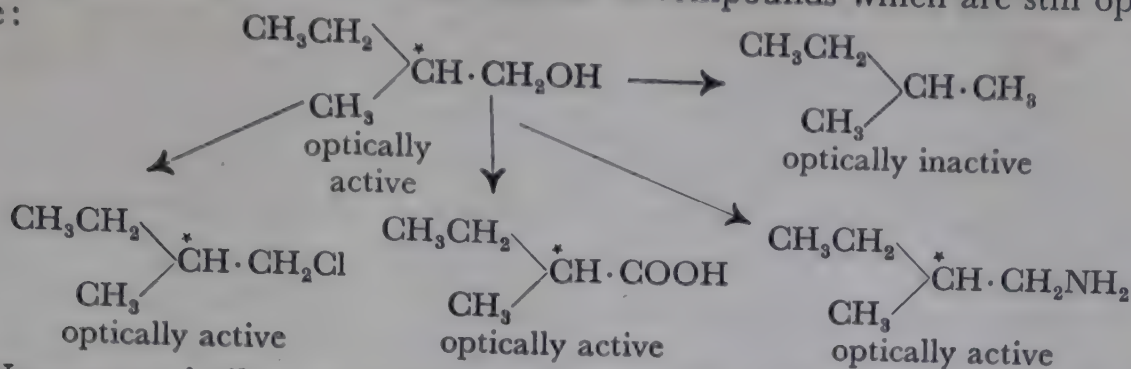
Molecules with an asymmetric carbon atom are completely unsymmetrical. They possess no elements of symmetry. The two enantiomorphous forms are mirror images of each other with respect to the plane aa' , but cannot be superimposed. The presence of an asymmetric carbon atom in the molecule of a compound always leads to an unsymmetrical arrangement.

Experience shows that optical activity is only produced when the molecule is completely unsymmetrical in structure. All chemical changes which remove the cause of the asymmetry of the molecule result in the disappearance of the optical activity. One is therefore led to the conclusion that *the capacity possessed by many substances of rotating the plane of polarization of light has its origin in their unsymmetrical molecular structure.*

If, for example, by the replacement of the hydroxyl group in optically active fermentation amyl alcohol by hydrogen, the asymmetric carbon atom, and with it the asymmetry of the whole molecule is removed, an optically inactive hydro-

¹ See J. H. VAN 'T HOFF, *Die Lagerung der Atome im Raum*, 3rd ed., Brunswick, (1903).

carbon is obtained, whilst all other reactions in which the asymmetry of the carbon atom is preserved result in the formation of compounds which are still optically active:



Numerous similar experiments have always given the same results. It is therefore believed that optical activity and asymmetry of the molecule are two inseparable phenomena. In general, the asymmetrical structure of an organic molecule is caused by an "asymmetric carbon atom" (such an atom being henceforth pointed out by an asterisk, C*), and it is therefore possible to tell from the structural formula of such a compound whether it will rotate the plane of polarization of light. There are, however, cases of substances which, although they lack an asymmetric carbon atom, have molecules in which there are no elements of symmetry (e.g. compounds of the allene type, 4-methylcyclohexylideneacetic acid, inositol, certain biphenyl derivatives). These are optically active. This shows that it is not merely the existence of a carbon atom attached to four different groups which is the cause of optical activity, but it is the *unsymmetrical structure of the molecule* which is the underlying cause, no matter how this asymmetry is produced.

Pasteur himself, to whom are due the first and fundamental observations of the optical activity of organic compounds (1859), and who discovered the methods of isolating optical isomerides, and the relations between optical activity and crystalline form, had already expressed the opinion that the differences between the antipodes had their origin in the different spatial structure of the isomerides. The above-mentioned considerations due to Le Bel and van 't Hoff have proved the certainty of it.

In enantiomorphic forms the corresponding groups of atoms are the same distance apart in the two isomerides. Hence, the affinity relationships of these groups in both antipodes must be the same. It is therefore to be expected that the physical and chemical properties due to the affinity relationships in the molecules will be the same for the two antipodes. This has been confirmed in the case of innumerable *d*- and *l*-forms, the chemical and physical properties of which have always proved to be identical. Differences can only be observed when the antipodes interact with other optically active systems (cf. p. 103 to 105).

In addition to the differences in optical behaviour, optical isomerides also show differences in crystallographic and physiological properties.

So far as the crystals of dextro- and lævorotatory forms have been accurately investigated it has always been found that they are hemihedral, the one form having a hemihedral face on the right, the other on the left.

The physiological properties of two antipodes can differ considerably. Thus, *d*-asparagine tastes sweet, *l*-asparagine is insipid (Piutti); *l*-nicotine is two or three times more poisonous than the *d*-form; *l*-adrenaline is much more active pharmacologically than is *d*-adrenaline. The cause of the different physiological behaviour of antipodes lies in the fact that many constituents of cells within the

organism with which the substances react are themselves asymmetric. If, for example, *l*-nicotine and *d*-nicotine combine with such an optically active cell constituent (*d*-B), two systems result:



which are not antipodes (the antipode of *l*-nicotine-*d*-B is *d*-nicotine-*l*-B), and being diastereoisomeric compounds must show different physical and chemical properties. Thus it is possible that the one isomeride might be a stronger poison than the other. Lower organisms (fungi, bacteria, etc.) are still more specific towards a definite configuration. This is carried so far that, in most cases, they attack and consume only one of the enantiomorphic forms, and leave the antipode completely unaffected.

If substances containing an asymmetric carbon atom are made by synthesis, it is always found that they are incapable of rotating the plane of polarization of light. This is due to the fact that such synthetic products always contain the dextro- and lævorotatory forms in equal amounts, the rotating power of one being compensated by that of the other. The reason for the formation of equimolecular mixtures of the *d*- and *l*-forms is the fact that the chemical and physical properties of the antipodes are equivalent. The conditions for the synthesis of lævo- and dextro-rotatory molecules are thus equally favourable, so that 50 per cent of each form is produced.

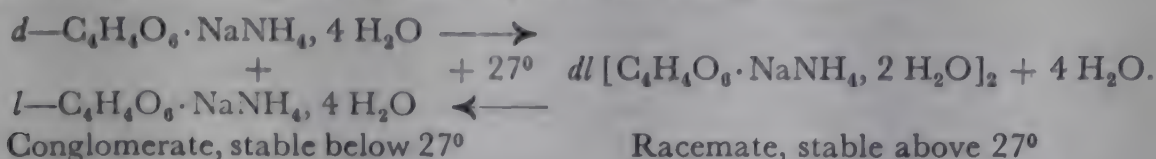
There are three types of inactive systems: 1. *Conglomerates* i.e. mechanical mixtures of crystals of the *d*- and *l*-forms (without chemical combination), 2. *Racemates*, i.e. molecular compounds of the two antipodes, and 3. *Pseudoracemic mixed crystals*, i.e. solid solutions of enantiomorphic substances without chemical combination.

The *racemate* is the most commonly occurring inactive system composed of *d*- and *l*-forms. The name was coined by Pasteur when he observed the phenomenon for the first time with tartaric acid (*acide racémique*) which is composed of dextro- and lævo-tartaric acid. Racemic compounds, so far as is known at present, are only stable in the solid state. In solution and in the vapour state they break down into their components, for their cryoscopic constant, conductivity, specific gravity, and chemical reactivity always agree with those of the optically active substances. The differences between racemates and optically active forms, apart from their behaviour towards polarized light and other asymmetrical systems, are therefore limited to properties of the solid phases. Thus, the melting point, density, and solubility may differ. Differences also appear in crystal form, the racemate being usually holohedral, and the optically active forms hemihedral. There may also be differences in the amount of water of crystallization associated with the molecule. Racemic tartaric acid crystallizes with 1 H₂O, whereas active tartaric acid is anhydrous. The calcium salt of inactive mannonic acid is anhydrous, whilst those of the active forms crystallize with 2 H₂O.

An inactive compound composed of dextro- and lævorotatory molecules is called a *dl*-form (or less frequently, an *i*-form).

Of the three inactive systems, racemate, conglomerate, and mixed crystal (solid solution), each may be stable throughout the whole temperature range in which it exists in the solid state, or it may be stable only within a certain temperature range, and at the limits of this range, transformation occurs into another inactive system. van 't Hoff, for example, has shown in the case of sodium ammonium

tartrate that above $+ 27^{\circ}$ the racemate is the stable substance in contact with the saturated solution, and below $+ 27^{\circ}$ the conglomerate:



Similar transitions are also possible between the racemate and the solid solution. The temperature at which the two forms are in equilibrium is called the transition temperature.

RESOLUTION OF INACTIVE FORMS INTO THEIR ACTIVE COMPONENTS. It has already been pointed out that all ordinary syntheses give rise to inactive products, and the problem of "resolving" the inactive mixture into the optically active forms is one which frequently occurs.

There are three chief methods of resolution:

1. **SPONTANEOUS RESOLUTION.** If the inactive form is a conglomerate, i.e. a mixture of *d*- and *l*-forms without combination, it is usually possible to separate it into the antipodes by crystallization, since these crystallize, as has been said above, in dextro- and lævo-hemihedral forms. If the crystals are sufficiently large and well-formed it is possible to separate them by hand-picking. The first conglomerate to be resolved was sodium ammonium tartrate, and the resolution was carried out by Pasteur by this method. The method is, however, very seldom applicable as it requires very good crystals, and conglomerates are few in number compared with racemates. Racemates cannot be resolved by this means. As they are molecular compounds they crystallize in only one form. Substances which occur both as racemates and as conglomerates can only be separated by crystallization in the temperature range in which the conglomerate is the stable form. In the case of sodium ammonium tartrate that is below 27° .

2. **BIOCHEMICAL RESOLUTION.** This is based on the observation made by Pasteur that fungi or bacteria which grow in solutions of racemic compounds and feed on them, almost invariably consume only one of the two enantiomorphic forms and leave the other. This provides the possibility of obtaining the unconsumed form in an optically pure state. *Penicillium glaucum*, for example, when placed in a solution of the ammonium salt of *dl*-tartaric acid, consumes the *d*-form and leaves the *l*-form. The same fungus destroys *l*-lactic acid, *l*-mandelic acid, *l*-aspartic acid, and *l*-leucine. It appears that a definite steric configuration must be present for a given organism to be able to assimilate the compound, and that optically active forms which are attacked by the same fungus under the same external conditions possess the same configurations. It is, however, possible gradually to accustom the fungus to the antipode.

In spite of the fact that biochemical resolution only allows the isolation of one of the optically active forms it has frequently been used for preparative purposes.

3. **CHEMICAL RESOLUTION.** The method most frequently used for the separation of racemic forms is chemical resolution, the principles of which are as follows: If a racemic compound is combined in some way or other with an optically active compound, for example, by salt formation, two products are obtained which are no longer antipodes. Suppose the problem is to resolve a racemic acid, tartaric acid. It is added to an optically active base, say the dextrorotatory alkaloid cinchonine, and a mixture of salts containing the two components [*d*-tartaric acid-*d*-cin-

chonine] and [*l*-tartaric acid-*d*-cinchonine] is obtained. These two salts are not antipodes, since the antipode of [*d*-tartaric acid-*d*-cinchonine] is [*l*-tartaric acid-*l*-cinchonine]. The salts produced must therefore possess different properties and different solubilities, and can be separated by fractional crystallization. Cinchonine *l*-tartrate is more difficultly soluble than cinchonine *d*-tartrate. When the salts have been completely separated by repeated crystallization, the cinchonine is split off by adding sodium hydroxide or a mineral acid, and pure *d*-tartaric acid is obtained from the one salt and *l*-tartaric acid from the other. This process is also due to Pasteur.

In a similar way, racemic bases can be resolved into their antipodes by using optically active acids.

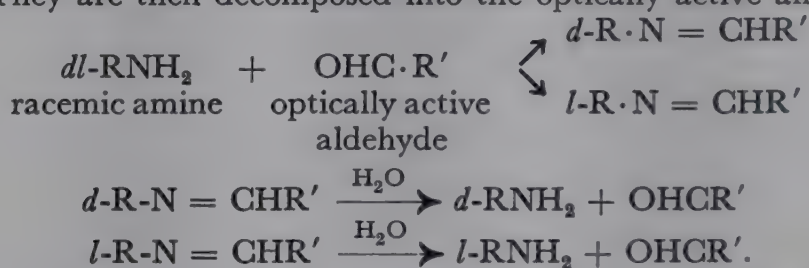
The most usual optically active acids and bases which are employed for such resolutions are:

Bases: Cinchonine, cinchonidine, quinine, quinidine, strychnine, brucine, morphine, optically active cobalt bases.

Acids: Tartaric acid, bromocamphorsulphonic acid, camphorsulphonic acid.

Instead of salt formation, other types of chemical combination can be used for the resolution of racemates, but they do not approach in practical importance the method described above. Erlenmeyer has combined amines with optically active aldehydes (e.g.

helicin, $\text{C}_6\text{H}_4 \begin{pmatrix} \text{O}(\text{C}_6\text{H}_{11}\text{O}_5) \\ \text{CHO} \end{pmatrix}$), obtaining aldimines which could be separated by fractional crystallization. They are then decomposed into the optically active amines:



Certain racemic alcohols (*dl*-terpineol, *dl*-tetrahydronaphthol) give molecular compounds with the optically active compound digitonin, which can be separated by fractional crystallization, and from these the optically active alcohols can be split off again (Windaus).

There are occasional exceptions where the chemical method of resolution fails. It happens here and there that the two salts which are produced from a *dl*-acid and an optically active base, or from a *dl*-base and an optically active acid, unite to form a molecular compound, which then crystallizes as a whole, so that, within the limits of its existence, a separation by fractional crystallization is impossible. These are examples of *partial racemates*. The following belong to this class:

d-methylsuccinic acid-*l*-quinine
l-methylsuccinic acid-*l*-quinine
 and
d-tartaric acid-*d*-tetrahydropapaverine
d-tartaric acid-*l*-tetrahydropapaverine

Partial racemates are, of course, optically active.

ASYMMETRIC SYNTHESSES. The above description has shown that in all syntheses in which optically active compounds might be produced, inactive systems containing 50 per cent of the *l*-form and 50 per cent of the *d*-form are actually obtained. The question of how the first optically active substance in nature was produced

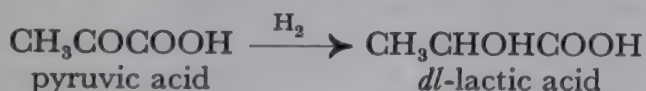
has often been debated at length without a full explanation having been arrived at. Pasteur already put forward the view that natural circularly polarized light might itself produce optically active substances in Nature. Their resolution is only possible with the aid of optically active substances. This view is supported by the recent experiments of Werner Kuhn, who was able to make α -bromopropionic acid ester and α -azidopropionic dimethylamide, $\text{CH}_3\text{CHN}_3\text{CON}(\text{CH}_3)_2$, optically active by irradiating them with right or left circularly polarized light. The effect is due to the fact that the right polarized light destroys one, the left polarized light the other component of the racemate more rapidly than the corresponding enantiomorphic form, so that the less attacked component remains in excess, thus endowing the chemically unchanged remainder of the compound with optical activity. The effects so far observed are rather small. By irradiation of α -azidopropionic dimethylamide with circularly polarized light of wave-length 3000 Å., preparations with specific rotations of $+0.78^\circ$ and -1.04° could be obtained.

The unequal absorption of circularly polarized light may also be used for syntheses of optically active compounds. Karagunis and Drikos observed that by the addition of halogen to triarylmethyls, $\text{R}'\text{R}''\text{R}'''\text{C}-$, under the influence of circularly polarized light, optically active substances were produced. Obviously under these conditions, one of the two enantiomorphic forms $\text{R}'\text{R}''\text{R}'''\text{C}\cdot\text{X}$ is formed in excess. M. Betti added chlorine to propylene in circularly polarized light and thus obtained optically active forms of 1 : 2-dichloropropane.

Asymmetry might also have been produced for the first time by the accidental crystallization of one optical antipode from a solution of a conglomerate, so leaving the rest of the solution optically active. To-day, however, it is not possible anymore to decide between this and other similar possibilities.

Much easier to carry out than *absolute asymmetric syntheses* are "*relative asymmetric syntheses*", which are performed with the aid of optically active substances. The principle underlying the method is illustrated by the following example:

If pyruvic acid is reduced, racemic lactic acid is formed:

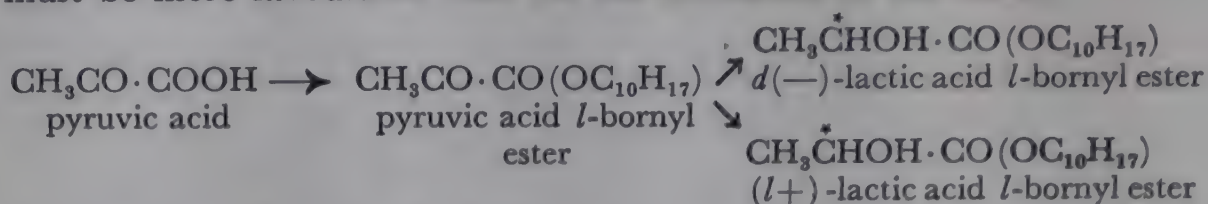


If however an active ester is prepared from the pyruvic acid by making it react with an optically active alcohol (say *l*-borneol), and this is reduced, the two possible isomers *d*(—)-lactic acid *l*-bornyl ester¹ and *l*(+)-lactic acid *l*-bornyl

¹ In recent times it has become usual in series of optically active substances which have analogous structures and are of known configuration (e.g. the α -amino-acids, and the α -hydroxy-acids) to call these, without regard to the actual sense of their rotation, *l*- or *d*-compounds, merely on the basis of their belonging to one or other of the steric series. In this case their actual optical rotation is given by the signs (+) or (—), which are put after the *l*- and *d*-. Thus all α -hydroxy-acids which have the —OH group in the same position in space are called *l*-acids, and their antipodes, *d*-acids; "*l*-lactic acid", $\text{CH}_3\text{CHOHCO}_2\text{H}$, actually rotates the plane of polarization to the right and is therefore called *l*(+)-lactic acid, whilst its antipode would be *d*(—)-lactic acid.

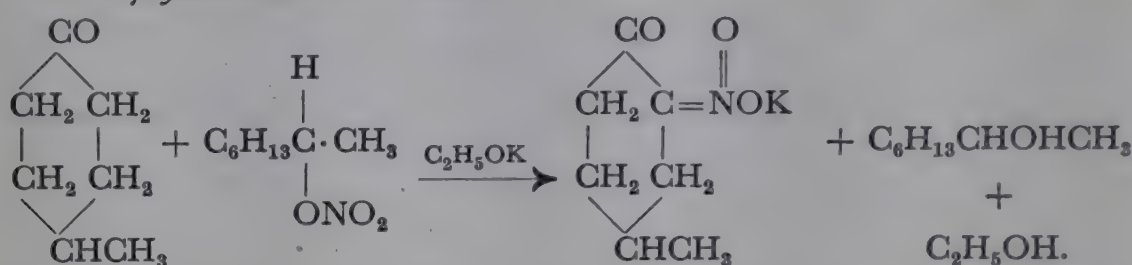
Another, new way of designating the two steric series, first used in the English-speaking countries, employs the letters *D* and *L* (small capitals), for the *d*-series and *l*-series respectively. Consequently, *d*(—)-lactic acid would be written as *D*-lactic acid and *l*(+)-lactic acid as *L*-lactic acid. The advantage of this nomenclature consists in avoiding doubt concerning the meaning of the letters (sense of rotation or indication of configuration).

ester, are not produced in equal quantities, the former being produced in excess (McKenzie). The two esters are not antipodes and therefore possess different chemical and physical properties, so that the conditions for the formation of the one must be more favourable than for the formation of the other.



If, after the reduction, the borneol is removed by hydrolysis, a lactic acid is obtained in which the $d(-)$ -form predominates. An "asymmetric" synthesis has thus been carried out.

Interesting asymmetric syntheses of another kind have been described by Shriner and Parker. If d -2-octyl nitrate is allowed to act upon inactive 1-methyl-*cyclohexanone*-(4), in the presence of potassium ethylate, an optically active potassium salt of the *aci*-form of 2-nitro-4-methyl-*cyclohexanone* is formed:



It is characteristic of all asymmetric syntheses that an optically active auxiliary system is introduced into the reaction, in order to obtain the products of the synthesis in the form of derivatives which are not antipodes, and which therefore have different chemical properties.

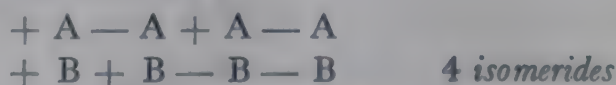
Experiments by Schwab and Rudolph indicate the possibility of carrying out asymmetric syntheses by another method. The break-down of racemic secondary butyl alcohol at copper deposited on optically active quartz is optically selective, i.e. under these conditions the one antipode is broken down more rapidly than the other. In this case, the optically active auxiliary system does not have an asymmetrical molecular structure but an asymmetrical structure of the crystal lattice. That such a lattice can act selectively was already known from the older work of Ostromisslensky, who proved that crystals of glycocholl (which crystallizes with hemihedral facets) could cause the crystallization of optically pure d - and l -asparagine in a supersaturated solution of asparagine.

According to W. Langenbeck, if two optically impure substances A and B combine by a bimolecular but *incomplete* reaction to give a new compound AB, there is an increase in the optical purity; the compound AB formed after prematurely stopping the reaction is thus optically purer than originally A and B. It is conceivable that relative asymmetric syntheses also take place according to this principle.

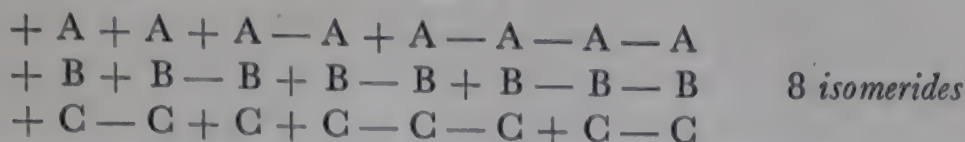
COMPOUNDS WITH MORE THAN ONE ASYMMETRIC CARBON ATOM. Up to the present only those substances have been considered which possess *one* asymmetric carbon atom, i.e. *one* asymmetric system in their molecules. The possibilities of isomerism become, of course, greater, and the relations more complicated if there is more than one asymmetric carbon atom.

Suppose the *structurally different* asymmetric carbon atoms are represented by A, B, C, etc., their dextrorotatory configuration with a +, and the lævorotatory configuration with a —. Then there are the following possible isomerides:

for two asymmetric carbon atoms

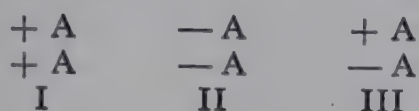


for three asymmetric carbon atoms



for four asymmetric carbon atoms the number of possible isomeric forms rises to 16, and for n asymmetric carbon atoms to 2^n . The 2^n stereoisomers belong to 2^{n-1} families of antipodes. Members of *different* families of antipodes show completely different chemical and physical behaviour since the distances, and with them the affinity relations of the corresponding groups of atoms, are different in the two isomerides.

Special relationships hold if some of the asymmetric carbon atoms of a compound are structurally identical. The number of possible stereoisomers is then less than 2^n , where n is the number of asymmetric carbon atoms. Suppose, for example, that there are two asymmetric carbon atoms of the same structure present. The three combinations



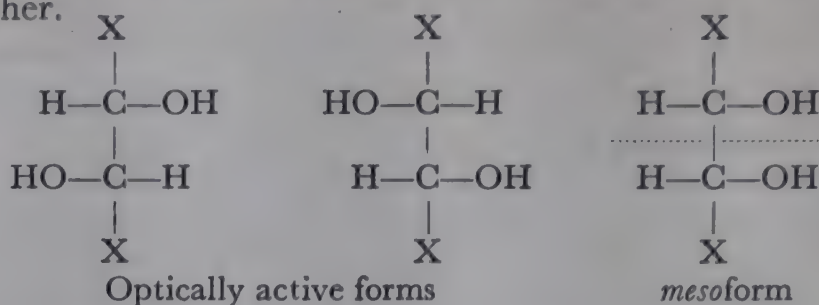
are possible. Compounds I and II are enantiomorphic forms and are optically active. In compound III, one of the optically active systems ($+A$) rotates to the right, and the other ($-A$) to the left, both to exactly the same extent, since both asymmetric carbon atoms are structurally identical. They must both exert an effect on the polarized light which is the same in amount, but different in sign. Compound III must therefore be inactive. It is however non-resolvable, since the inactivity is not, as in the case of the racemates, due to *intermolecular* compensation, but to the opposing effects of two halves of the same molecule. Such a form is said to be internally compensated (*intramolecular* compensation). It is also called a *mesoform*.

A molecule in which the one half has a $+$ configuration and the other half, which is structurally identical, has a $-$ configuration must be symmetrical. The two halves behave like non-superposable mirror images. The inactivity, which in the case of the racemates is due to the occurrence together of two asymmetrical molecules to give a symmetrical molecular compound, is here due to the two asymmetric *halves* of the molecule giving together a symmetrical molecule. The phenomenon of internal compensation will often be met with again later on in this book, and its connection with other stereochemical questions and space isomerism will be discussed.

In order to represent the configuration of such molecules on paper, the so-called *projection formulæ* proposed by E. Fischer are generally used. These are obtained by imagining the carbon tetrahedra which are linked in a chain to be opened out into a straight line so that all the groups are projected on to the plane of the paper. The groups of atoms combined with the carbon atoms then lie to the right and the left of the straight line in which the carbon atoms lie, and from these projection formulæ a picture of the mutual positions of the groups in space is obtained.

Such projection formulæ make it clear at a glance whether a molecule is symmetrical or not. The symmetrical *mesoform* can be cut by a plane of sym-

metry into two equal parts which stand in the relationship of object and mirror image to each other.



Higher alcohols. Various of the higher saturated alcohols are found in nature, chiefly in the form of esters. The middle alcohols are found in this form in essential oils, and the highest in waxes.

Primary n-hexyl alcohol is met with as an ester in the essential oil of the seeds of *Heracleum giganteum*, an isomeride, $(\text{C}_2\text{H}_5)(\text{CH}_3)\text{CHCH}_2\text{CH}_2\text{OH}$, in Roman camomile oil, and *d*-4-methyl-pentanol-2 in Réunion geranium oil. Esters of *n*-OCTYL ALCOHOL are present in the essential oils of various species of *Heracleum*, and those of primary *n*-NONYL ALCOHOL in the oil of orange skins, *n*-octanol-3 in the essential oil of *Mentha pulegium* L. A DODECYL ALCOHOL, $\text{C}_{12}\text{H}_{26}\text{O}$, is found as esters of the higher fatty acids in the oil of *Cascara sagrada*, and an alcohol, $\text{C}_{13}\text{H}_{28}\text{O}$, is found in bananas.

Numerous alcohols of the series from C_6 to C_{15} have been obtained by synthesis.

The alcohols present in waxes are more important. These include CETYL ALCOHOL, $\text{CH}_3(\text{CH}_2)_{14}\text{CH}_2\text{OH}$, which, in the form of its palmitic ester is the chief constituent of spermaceti. It gives palmitic acid on oxidation. CERYL ALCOHOL, $\text{C}_{26}\text{H}_{53}\text{OH}$ is found in many plants, and also combined with cerotic acid in Chinese wax (which contains in addition the alcohol with 28 carbon atoms), as an ester in the sweat of sheep, in Carnauba wax, bees wax, and the wax of the flax plant.

In bees wax and Carnauba wax MYRICYL ALCOHOL, or MELISSYL ALCOHOL, $\text{C}_{31}\text{H}_{63}\text{OH}$, is also found, usually as its palmitic ester. Alcohols with 32 and 34 carbon atoms are also present in Carnauba wax. The wax from wheat contains *n*-octacosanol, $\text{C}_{28}\text{H}_{57}\text{OH}$, and that from lucrene, *n*-triacontanol, $\text{C}_{30}\text{H}_{61}\text{OH}$.

The alcohols of the waxes are solid at ordinary temperature.

For the synthesis of higher fatty alcohols, see page 197.

Unsaturated alcohols. In the case of the unsaturated halogen compounds, where the halogen atom may be attached either to a carbon atom linked to another by a double bond, or to one linked with a single bond, it will be remembered that the position of the halogen atom greatly influences the properties of the compound. The same is true of the position of the hydroxyl group in the unsaturated alcohols.

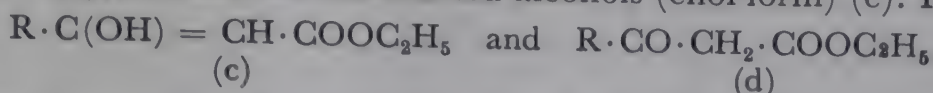
Unsaturated alcohols with the *hydroxyl group attached to an unsaturated carbon atom* are, in the case of the simple, monohydric, aliphatic alcohols, in general unstable. In reactions which should lead to their formation, rearrangement to the isomeric forms (b) takes place.



Thus, the simplest possible unsaturated alcohol, VINYL ALCOHOL, $\text{CH}_2 = \text{CHOH}$ is not yet known. Whenever it should be formed, the isomeric compound acetaldehyde, CH_3CHO , is produced (stable esters and ethers of vinyl alcohol, $\text{CH}_2 = \text{CHOCOR}$ and $\text{CH}_2 = \text{CHOR}$, however, do exist).

The view formerly held that a hydroxyl attached to a doubly linked carbon

atom could not exist at all, is not strictly accurate. It is now known that there are many substances usually, however, of more complex structure, or containing a number of oxygen atoms, which are stable and can be isolated not only in the carbonyl (or keto) form (d), but also as unsaturated alcohols (enol form) (c). For example:

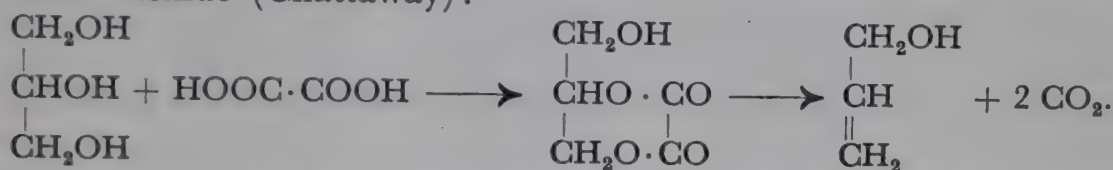


However, the conditions under which the simplest, monohydric, unsaturated alcohols would be stable are not yet known.

The isomerism between a carbonyl compound and an unsaturated alcohol (*enol* form) produced from it by the wandering of a hydrogen atom is called *tautomerism* or *desmotropism*. By tautomeric or desmotropic forms is understood those which through the change of linking of individual atoms are easily converted into one another; for example, the hypothetical vinyl alcohol, $\text{CH}_2 = \text{CHOH}$, is the enol form of acetaldehyde, CH_3CHO , the carbonyl, or keto form. They are "tautomers" or "desmotropes".

Liquid mixtures of tautomeric forms, in which the two isomers are in equilibrium, have been called by Knorr, *alлетropic* mixtures.

Of the simpler unsaturated alcohols, ALLYL ALCOHOL is the easiest to prepare, and has therefore been investigated most thoroughly. It is formed in good yield by heating glycerol with oxalic (or formic) acid. A neutral glyceryloxalate is produced as an intermediate product, and on further heating breaks down to allyl alcohol and carbon dioxide (Chattaway):



The constitution of allyl alcohol is derived from its unsaturated character which is shown, for example, in its capacity to add two halogen atoms, or two hydrogen atoms. Also, allyl alcohol is oxidized to an unsaturated aldehyde (acrolein), and an unsaturated acid (acrylic acid), proving the presence in it of a primary alcohol group, CH_2OH . The catalytic reduction of allyl alcohol with hydrogen in the presence of platinum (or nickel) leads to the formation of normal propyl alcohol.

• Allyl alcohol boils at 96° .

Alcohols of the formula $\text{C}_n\text{H}_{2n+1}\text{CHOH} \cdot \text{CH} = \text{CH}_2$ easily rearrange into those of the structure $\text{C}_n\text{H}_{2n+1}\text{CH} = \text{CHCH}_2\text{OH}$, and both give the primary bromide $\text{C}_n\text{H}_{2n+1}\text{CH} = \text{CHCH}_2\text{Br}$ on treatment with hydrogen bromide. The bromide can be reconverted into the two isomeric alcohols (Ch. Prévost). Other allyl derivatives in which there is a mobile substituent X (Cl, CN, etc.) also undergo this allyl rearrangement:

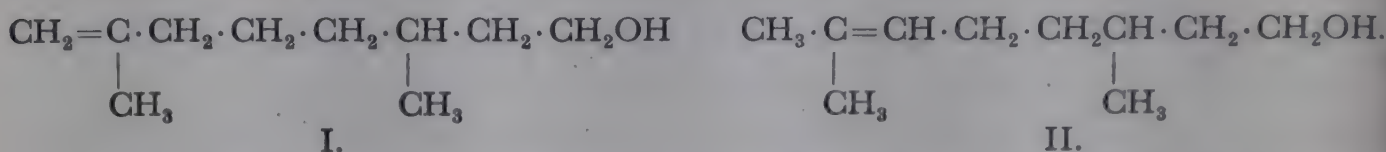


Some higher, mono- and dihydric unsaturated alcohols are found in the essential oils of different plants. They are characterized by a strong pleasant odour, and are the chief odoriferous principles of the essential oils of those plants. In constitution they show relationships with the terpenes and camphors, into which they can easily be transformed, but they differ from them in not possessing a cyclic structure.

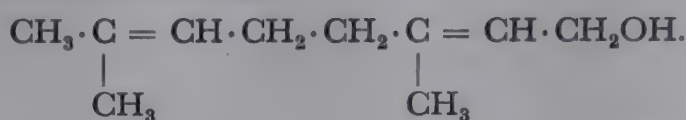
CITRONELLOL is present in many plants, and is almost always accompanied by geraniol. In rose oil it occurs as the *lævorotatory* form, in citronella oil as the *dextrorotatory* form, and in geranium oil as both enantiomorphic forms. *d*-Citro-

nellol is made artificially by the reduction of the aldehyde citronellal with sodium amalgam or aluminium amalgam (Dodge, Tiemann, and Schmidt). It has the odour of roses. Its boiling point is 117°–118° (17 mm).

The constitution of citronellol corresponds to formula I. It is 2 : 6-dimethylocten-(1)-ol-(8). On ozonolysis some acetone is, however, always formed, from which it is concluded that either during the ozonization a partial wandering of the double bond occurs, or else the natural product contains a certain quantity of the isomeric *rhodinol*¹, i.e. 2 : 6-dimethylocten-(2)-ol-(8), formula II.



The *cis-trans* isomeric alcohols GERANIOL and NEROL, which contain two double bonds, have the structural formulæ



Geraniol is the chief constituent of rose oil, geranium oil, palmarosa oil, citronella oil, and lemongrass oil. Nerol is found in neroli oil, and oil of bergamot, amongst others. Both alcohols are formed (in addition to terpeneol) from linalool by an intramolecular displacement of the alcohol group and the double bond, when *linalool* (see below) is warmed with acetic anhydride (Barbier, Bertram, Gilde-meister). Geraniol is also easily obtained by the reduction of the natural aldehyde, citral, $(\text{CH}_3)_2\text{C}=\text{CH}\cdot\text{CH}_2\cdot\text{CH}_2\text{C}=\text{CH}\cdot\text{CHO}$ (Tiemann).

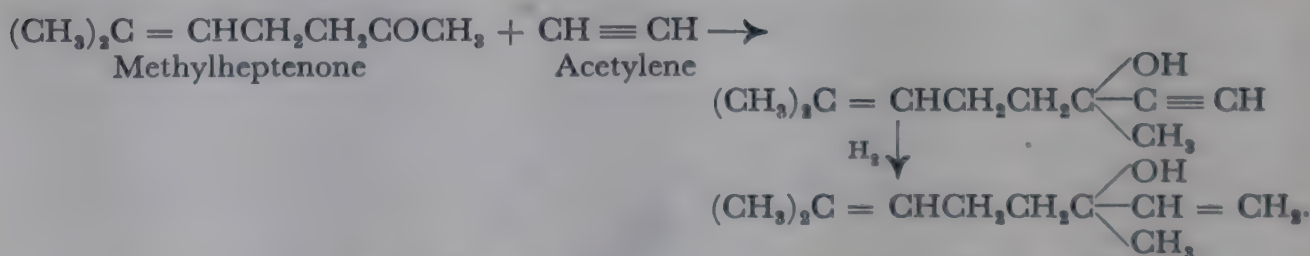


Nerol can be prepared by the isomerization of geraniol on heating with alcoholates.

Both alcohols are valuable perfumes with a rose-like odour. Their odours are, however, quite distinguishable. LINALOOL, isomeric with geraniol and nerol, possesses a smell recalling lilies of the valley, and is a valuable perfume (as is also its acetic ester). Its constitution corresponds to the formula:



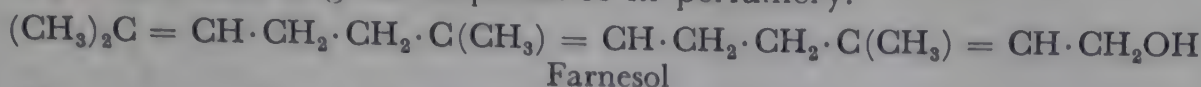
Linalool occurs in linaloe and coriander oil, in oil of bergamot, oil of lavender, and other oils. It is optically active, and is obtained in the inactive form by the isomerization of geraniol (Schimmel) and from methylheptenone by the following route (Ruzicka):



On account of its lasting and pleasant smell of lilies of the valley, *farnesol*,

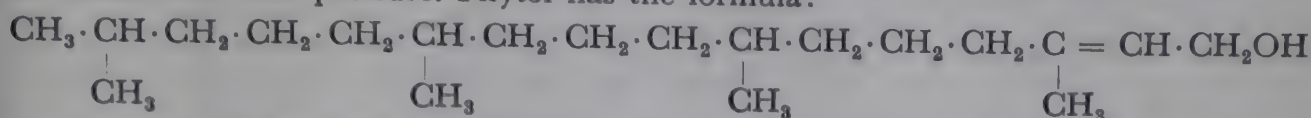
¹ The name "rhodinol" is occasionally also used for lævorotatory citronellol.

an alcohol with three double bonds found in oil of ambrette seed and in lime flowers, etc., is also of great importance in perfumery.

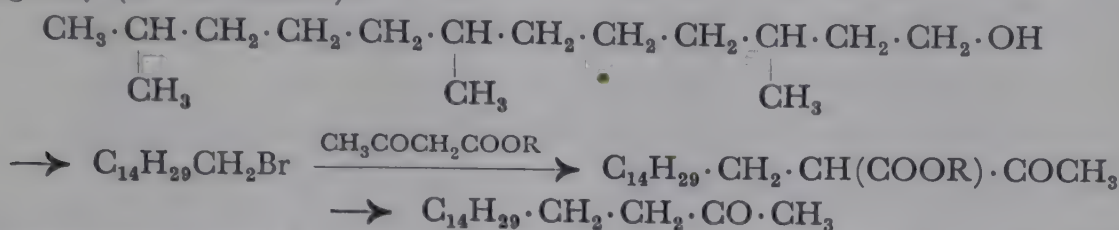


The compound can also be obtained synthetically.

Another unsaturated aliphatic alcohol with an ethylenic linkage is PHYTOL, $\text{C}_{20}\text{H}_{40}\text{O}$, which Willstätter has shown to be a constituent of chlorophyll. It is a thick oil which boils at 145° under 0.03 mm pressure. Phytol has the formula:



since ozonization followed by hydrolysis gives glycolaldehyde and a ketone $\text{C}_{18}\text{H}_{36}\text{O}$, which proves to be identical with a ketone synthesized from hexahydrofarnesol in the following way (F. G. Fischer):



Few representatives of alcohols with triple bonds are known. The simplest compound of this type is PROPARGYL ALCOHOL $\text{CH} \equiv \text{C} \cdot \text{CH}_2\text{OH}$, which can be obtained from bromoallyl alcohol by heating with caustic potash or soda (Henry). The reaction does not, however, proceed very smoothly:



Propargyl alcohol boils at 114° – 115° , and being a derivative of acetylene gives difficultly soluble heavy-metal salts. The white, explosive, and photo-sensitive silver salt, and the yellow cuprous salt are characteristic.

Esters of the alcohols with inorganic acids

The alkyl esters of the mineral acids can be prepared in various ways. In many cases the classical method of esterification — the interaction of an acid with an alcohol — of which the mechanism has already been described, is suitable. An example is the formation of an alkyl hydrogen sulphate from an alcohol and sulphuric acid:



The reaction between inorganic salts and alkyl halides or dialkyl sulphates provides a smooth method of synthesizing esters:



Finally, a method which is much used for the preparation of the alkyl esters of mineral acids is to act upon the alcohol with the acid chloride:



Esters of the halogen hydracids, the alkyl halides, have already been considered (p. 72 ff).

Esters of nitrous acid. These are formed by the action of nitrogen trioxide (nitrous anhydride) on alcohols:



The synthesis from nitrosyl chloride and an alcohol may be regarded as a modification of this method, pyridine being added to retain the hydrogen chloride formed in the reaction (Bouveault). Esters of nitrous acid and the isomeric nitro-

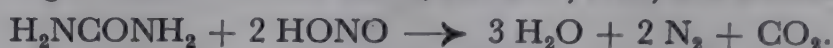
compounds are formed together by the action of silver nitrite on an alkyl halide.

ETHYL NITRITE and AMYL NITRITE are of importance. They are volatile liquids with a stupefying odour. They accelerate the pulse and lower the blood pressure, and are therefore used in therapeutics for the treatment of asthma and angina pectoris. The ease with which the alkyl nitrites break down into nitrous acid and alkyl derivatives is noteworthy. They are therefore often used in place of nitrous acid for introducing the nitroso-group into other substances (preparation of nitroso-compounds and diazonium salts).

Esters of nitric acid. The *alkyl nitrates* are usually prepared by the action of concentrated or fuming nitric acid on alcohols:



The small amount of nitrous acid always formed owing to oxidation reactions, and which would give rise to nitrous esters, is destroyed by the addition of some urea:



The esters of nitric acid are mobile liquids with a pleasant smell, which explode violently on overheating (care required in distillation). The nitric esters of the polyhydric alcohols, such as *nitroglycerol*, and *nitrocellulose* (nitric ester of cellulose) are of tremendous practical importance as explosives. They will be considered again later.

Esters of hypochlorous acid. The esters of hypochlorous acid, discovered by Sandmeyer, are formed by the action of chlorine on alcohol solutions of sodium hydroxide.

As the esters are easily decomposed on exposure to light, the preparation must be carried out in the dark.

The *methyl ester* is gaseous at ordinary temperatures (b.p. 12°). The *ethyl ester* is a yellow oil (b.p. 36°). Methyl hypochlorite explodes violently on ignition, and the ethyl ester explodes when overheated.

Esters of sulphuric acid. As sulphuric acid is dibasic it gives two series of esters: the *acid esters*, also known as *alkyl sulphuric acids* or *alkyl hydrogen sulphates*, $\text{C}_n\text{H}_{2n+1}\text{O}\cdot\text{SO}_2\text{OH}$, and neutral esters, or *dialkyl sulphates*, $(\text{C}_n\text{H}_{2n+1})_2\text{SO}_4$.

The *alkyl hydrogen sulphates* are produced by the action of concentrated sulphuric acid on alcohols. The process is reversible and the formation of the ester is therefore never quite complete:



The alkyl hydrogen sulphates can be separated from the excess of sulphuric acid as the barium or calcium salts, which (in contrast to BaSO_4 and CaSO_4) are easily soluble in water.

Other methods of preparing alkyl hydrogen sulphates depend on the action of chlorosulphonic acid on alcohols, and the addition of sulphuric acid to olefins:



The free alkyl hydrogen sulphates, which can be liberated from their barium salts by the addition of the calculated quantity of sulphuric acid, are syrupy, hygroscopic liquids, easily soluble in water, and possessing a strongly acid reaction. In their properties they thus show much similarity to sulphuric acid itself. Their salts crystallize well. Formerly, the alkali-metal salts particularly were often used

as alkylating agents, since they readily give up the alkyl group to other compounds. In more recent times they have been almost entirely superseded in this respect by the dialkyl sulphates, the alkyl halides, and the esters of toluenesulphonic acid.

The alkali salts of acid sulphuric acid esters of higher alcohols possess soap-like properties, and can be obtained either by esterification of synthetically prepared higher fatty alcohols (see p. 197) or by adding sulphuric acid on to higher olefins. Compared with ordinary soaps they have the advantage of not forming precipitates with hard water, since their Ca and Mg salts are soluble in water. They are extensively used, particularly in the textile industry.

Of the *neutral sulphuric esters*, dimethyl sulphate $(\text{CH}_3)_2\text{SO}_4$, and diethyl sulphate $(\text{C}_2\text{H}_5)_2\text{SO}_4$, are technically important as alkylating agents. They can be prepared by distilling the calculated quantity of sulphur trioxide into cooled methyl or ethyl alcohol:



or, methyl hydrogen sulphate can be decomposed by distillation *in vacuo* into dimethyl sulphate and sulphuric acid:



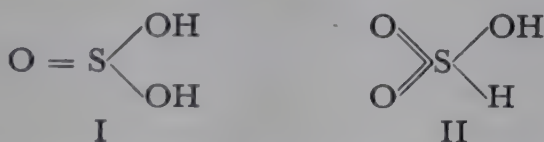
DIMETHYL SULPHATE is a colourless oil, immiscible with water, boiling at 187° . The compound is highly toxic. It causes inflammation of the skin; it irritates the respiratory organs, can lead to paralysis, and is often fatally poisonous.

DIETHYL SULPHATE is also poisonous (b.p. 96° at 15 mm).

The higher dialkyl sulphates are best prepared from the chlorosulphonic esters and dialkyl sulphites:

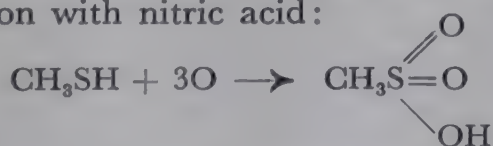


Esters of sulphurous acid. Sulphurous acid is a tautomeric inorganic acid. Some of its inorganic salts are derived from the formula I and others from formula II:

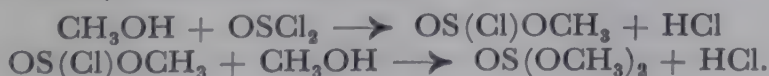


Some of its organic derivatives have the symmetrical form I, and some the unsymmetrical form II. Compounds of the latter type, the *alkylsulphonic acids*, are obtained in the form of salts or esters by the action of alkyl halides on sulphites (cf. p. 123).

Their constitution is determined by the fact that they are obtained from mercaptans by oxidation with nitric acid:



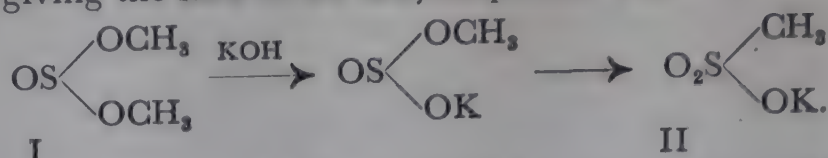
The neutral esters of the symmetrical form of the acid, the *alkyl sulphites*, are formed from thionyl chloride and alcohols:



If another alcohol is used in the second stage of the reaction, unsymmetrical di-esters can be produced (W. Voss).

The alkyl sulphites are aromatic smelling liquids (methyl ester boils at 121° , the ethyl ester at 161°), which have recently been recommended for the alkylation

of phenols, alcohols, and acids in a non-alkaline medium. On alkaline hydrolysis they rearrange giving the salts of the alkylsulphonic acids:



Esters of phosphoric acid. The tertiary phosphoric esters can be prepared by the action of silver phosphate on alkyl halides, or of phosphorus oxychloride on alcohols.



If smaller quantities of alcohol are used in the latter reaction, primary and secondary phosphoric esters may also be obtained. The trialkyl phosphates are neutral liquids which can be distilled without decomposition (methyl ester boils at 193° and the ethyl ester at 216°). The acid esters are hygroscopic substances, soluble in water, which give crystalline salts.

Alkyl and aryl esters of phosphoric acid are used as substitutes for camphor in the manufacture of cellulose esters.

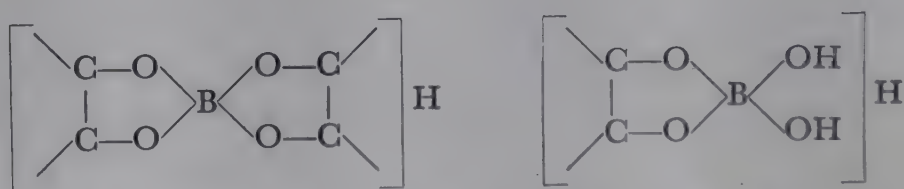
Esters of boric acid, $\text{B}(\text{OC}_n\text{H}_{2n+1})_3$. These esters are formed remarkably easily by warming alcohol with boric anhydride or boron trichloride. The lower trialkyl esters of boric acid are volatile liquids which burn with a green flame (qualitative test for boric acid). They are rapidly hydrolysed by water.

Their behaviour towards alcohols is very interesting. They combine with them to form complex alkoxo acids, which are comparable in strength with other organic acids, and form stable salts (H. Meerwein):



In this reaction the alkyl borates act like acid anhydrides, combining with the anions of the solvent, alcohol, and thus increasing the hydrogen ion concentration.

Certain polyhydric alcohols (glycerol, erythritol, mannitol, sorbitol, dulcitol, etc.) react remarkably easily with boric acid forming complex compounds, in which the boric acid appears to be united with the alcohols giving negative complex ions. Böeseken considers them to be complexes of one of the following formulæ:



The anion forms a tetrahedron with the boron atom at its centre.

Practical use is made of these compounds between boric acid and alcohols. They are stronger acids than boric acid itself. It is therefore possible to titrate boric acid, after addition of one of the above polyhydric alcohols, as a monobasic acid.

Esters of silicic acid. The neutral esters of orthosilicic acid may be prepared from silicon tetrachloride and alcohol:

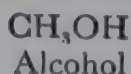


They possess pleasant smells, are difficultly soluble in water, and are broken down on warming with water into silicic acid and alcohol. Their low boiling points are somewhat surprising when the involatility of silicic acid is considered. The tetramethyl ester boils at 122° , the ethyl ester at 165° . The ethyl ester of meta-

silicic acid, on the other hand, is much more difficultly volatile (b.p. 360°). This may be due to its being a polymeric substance like silicic acid itself, and it may, perhaps, be written $((\text{C}_2\text{H}_5\text{O})_2\text{SiO})_x$, whilst the tetraalkyl esters of orthosilicic acid, in which there is no $\text{Si}=\text{O}$ group, are monomolecular.

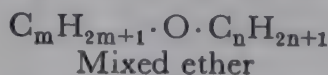
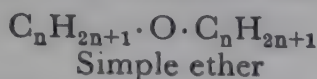
Ethers

If the alcohols are regarded as the monoalkyl derivatives of water, the ethers may be considered as the dialkyl derivatives of water:



If, however, the organic radicals are regarded as the foundation of the molecule, it is evidently also correct to call the ethers alkyl oxides, and to compare them with the metal oxides.

There are two classes of ethers, *simple* ethers and *mixed* ethers, according as two identical or two different alkyl radicals are present in the molecule:



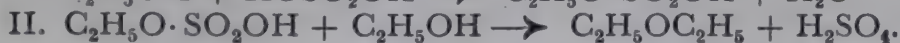
PREPARATION. Williamson's synthesis of ethers is conclusive as regards the constitution of these compounds. The reaction between alkyl halides and sodium alcoholates is used:



It is clear that both symmetrical and unsymmetrical ethers can be obtained in this way. Ethers can also be prepared smoothly from alkyl halides and silver oxide:



The process used technically to prepare ethers, particularly diethyl ether, uses alcohol and sulphuric acid as starting materials.¹ As a result of extensive studies, particularly by Williamson, the course of the reaction is clear in its essential details. In the first stage, the alcohol reacts with the sulphuric acid to form an alkyl hydrogen sulphate and water. Then, on heating, the alkyl hydrogen sulphate reacts with a second molecule of alcohol. The ether is thus produced and sulphuric acid is regenerated.



If another alcohol from that used to obtain the alkyl hydrogen sulphate is added in the second stage (II), a mixed ether is formed. This fact is a proof that the reaction actually does take place in the two stages. It is obvious from the equations that the same amount of sulphuric acid is regenerated as is used up. It is not possible, however, to produce an unlimited quantity of ether with a small quantity of sulphuric acid, owing to side reactions, which, running concurrently with the main reaction, finally bring it to a stop. Thus, the water formed in the reaction only distils over to a small extent with the ether. The remainder stays in the distilling vessel and, as its concentration increases decomposes the alkyl hydrogen sulphate (or counteracts its formation). The reaction, therefore, comes eventually to a complete stop. A part of the sulphuric acid is lost by reduction to sulphurous

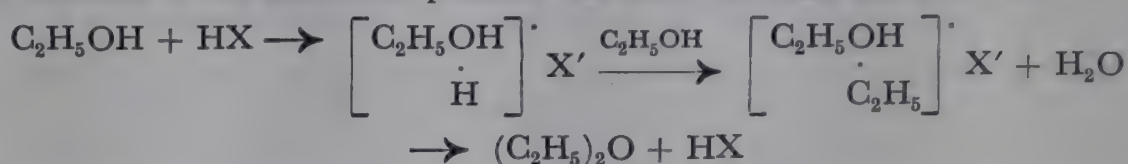
¹ The process is only suitable for the preparation of the first three members of the series. The higher alcohols split off water intramolecularly on heating with sulphuric acid and give unsaturated hydrocarbons in addition to ethers. However, *isoamyl* ether is prepared in this way, though the yield is only 12–13 per cent.

acid. Also ethanesulphonic acid is sometimes produced as a result of further side reactions.

According to J. van Alphen the formation of ethers does not necessarily take place with the intermediate formation of alkyl hydrogen sulphates, since other strong acids, e.g. hydrochloric acid or acid salts, can bring about the reaction in place of sulphuric acid. The formation of ether is regarded as a reversible reaction:



which is catalysed by hydrogen ions. It would thus belong to the same type of reaction as the formation and hydrolysis of acetals and esters. The catalytic action of acids in the formation of ethers has been explained by H. Meerwein in the following way: The acid first adds on to the alcohol with formation of an oxonium salt, which then reacts with a second molecule of the alcohol to produce the ether oxonium salt and water:



(For oxonium salts, cf. below).

For the preparation of ordinary diethyl ether the distillation vessel is filled with 5 parts of alcohol and 9 parts of sulphuric acid, and the whole heated to 130°–140°. Ether, together with some water, distils. During the distillation, alcohol is run into the vessel at the same rate as the ether distils until the sulphuric acid is exhausted, i.e. is no longer able to produce more ether. According to a new method, due to Senderens, ethers are also obtained if alcohol vapour is passed over alumina heated to 240–260°.

PROPERTIES. The ethers are pleasant “ethereal” smelling liquids, which are difficultly soluble in water, but easily soluble in organic liquids. The lower members are very volatile. All have a considerably lower boiling point than the alcohols with the same number of carbon atoms. The cause of this is that the alcohols, like water whose hydroxyl group they still contain, are strongly associated, whilst the ethers are monomolecular. The ethers do not contain the hydroxyl group, upon which the association of alcohols and water depends.

Ether		b.p.	Normal primary alcohol	b.p.
Dimethyl ether	$\text{C}_2\text{H}_6\text{O}$	— 23.6°	Ethyl alcohol	78°
Diethyl ether	$\text{C}_4\text{H}_{10}\text{O}$	+ 34.6°	Butyl alcohol	117°
Dipropyl ether	$\text{C}_6\text{H}_{14}\text{O}$	+ 90.7°	Hexyl alcohol	157°
Di- <i>n</i> -butyl ether	$\text{C}_8\text{H}_{18}\text{O}$	+ 141°	Octyl alcohol	195°

The atomic refraction of oxygen in ethers is 1.643 (D line) and is thus considerably higher than that of oxygen in the hydroxyl group (1.525).

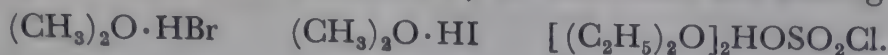
The ethers are rather stable substances, more so than the alcohols. They do not react with the alkali metals, indeed sodium is used to dry ether. They are very resistant towards alkalis. On the other hand they are easily decomposed by acids, particularly the halogen hydracids, of which hydriodic acid is the most effective. This reagent attacks the ether in the cold, converting it into an alkyl iodide and alcohol:



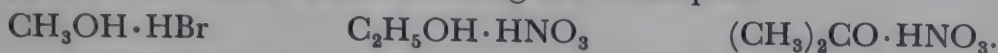
At a higher temperature the alkyl iodide is the only product:



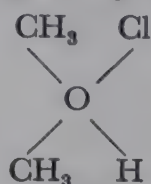
Of great theoretical interest are the addition compounds which the ethers form with the halogen hydracids, other acids, and metal salts. Friedel described the first simple substance of this kind, the addition compound of dimethyl ether and hydrogen chloride, $(\text{CH}_3)_2\text{O} \cdot \text{HCl}$. Since then, many similar substances have been prepared, of which those obtained by D. McIntosh are among the simplest:



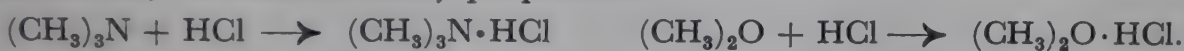
The ethers are, however, not the only oxygen-containing organic substances which tend to form such molecular compounds. It was shown by Baeyer and Villiger that alcohols, aldehydes, ketones, and acids can also form addition products with metal salts and acids.¹ The phenomenon is observed even with very simple oxygen compounds. The following are examples:



As regards the constitution of these addition products, it was suggested by Friedel, and particularly by Collie and Tickle, that they should be regarded as compounds containing *tetravalent oxygen*, e.g. as indicated by the formula:



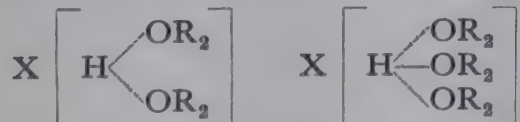
As they are salt-like in character, and the salt formation takes place at the oxygen atom, they have received the name "*oxonium salts*". There is, in fact, a close analogy, between ammonium salts and oxonium salts, not only in the method of formation, but also in many properties.



The formulation of oxonium salts with tetravalent oxygen does not, however, explain sufficiently well a number of different phenomena observed with these salts. Particularly, it gives no explanation of the existence of numerous "*anomalous*" oxonium salts, in which the ether and acid are not combined in the proportion 1:1, but in other ratios. The addition compounds of ethers with metal salts are also difficult to explain on the assumption of tetravalent oxygen. It is therefore better to regard the oxonium salts, according to A. Werner, as *coordination compounds*, just as in the case of the ammonium salts. The oxygen of the ethers, alcohols, ketones, aldehydes, etc. is unsaturated and is capable of adding on acids or metal salts. They thus form oxonium salts, which are composed of the complex oxonium ion (comparable to the ammonium ion), and the negative acidic ion:



The "*anomalous*" oxonium salts are then formulated as follows:

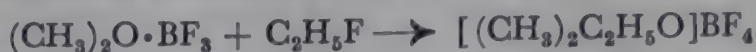


This explanation makes it possible to include the extremely numerous hydrates of different types of compounds as oxonium salts. (For the electronic formulation of oxonium salts, see p. 125).

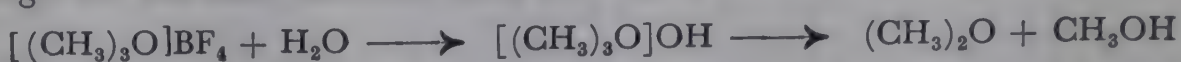
Until recently only those oxonium salts were known which are formed by the addition of *acids* to ethers. Of late, H. Meerwein has, however, succeeded in

¹ See P. PFEIFFER, *Organische Molekülverbindungen*, Stuttgart, (1927).

preparing tertiary oxonium salts in which three alkyl radicals are combined with the oxygen. For example, such trialkyloxonium salts are formed from the addition products of boron trifluoride and ether, and alkyl fluorides:



The trialkyloxonium boron fluorides are solid, salt-like, very reactive compounds. They are powerful alkylating agents and decompose with water, through the unstable oxonium bases into ether and alcohol:



Dimethylether, $(\text{CH}_3)_2\text{O}$. This is usually prepared from methyl alcohol and concentrated sulphuric acid or phosphoric acid. It is a colourless gas.

Diethyl ether, $(\text{C}_2\text{H}_5)_2\text{O}$. This is also called *ethyl ether*, or simply *ether*. Its preparation from ethyl alcohol and sulphuric acid has already been described. It is a mobile liquid, very easily inflammable, and readily volatile (b.p. 34.6°). Mixtures of ether vapour and air are explosive. Ether is somewhat soluble in water. 100 parts of water dissolve 7.5 parts by weight of ether at 16° . Ether also dissolves some water (1–1.5 per cent at room temperature).

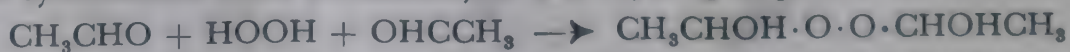
Ether is an excellent solvent for fats, resins, and many other organic substances. Since it mixes only slightly with water it can be used to extract substances dissolved in water. Besides its use as a solvent and an extracting agent it is used in industry in the manufacture of smokeless powder (gelatinization of nitrocellulose) and in the preparation of Chardonnet artificial silk, and collodion. Its great latent heat of evaporation is occasionally made use of in the production of low temperatures. Mixtures of solid carbon dioxide and ether give temperatures as low as -80° . In medicine, ether is used as an anæsthetic. For this purpose it must be specially pure.

Ethyl ether combines fairly easily with acids, metal salts, etc., to give oxonium compounds. Upon this fact depends the great solubility of ether in concentrated hydrochloric and sulphuric acids, and the solubility of hydrogen chloride gas in ether. With bromine it forms the addition products $(\text{C}_2\text{H}_5)_2\text{O} \cdot \text{Br}_2$ and $(\text{C}_2\text{H}_5)_2\text{O} \cdot \text{Br}_3$. Amongst the very numerous addition products with metal salts the following may be mentioned:

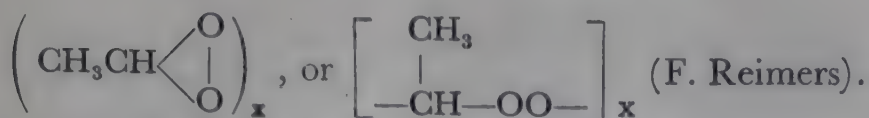


Ether is oxidized even by atmospheric oxygen on long standing, and then contains peroxidic substances. This can easily be shown by adding ether, which has been allowed to stand in the air for some time, to a solution of a pure ferrous salt and potassium thiocyanate. The peroxides present oxidize the ferrous salt to the ferric state, and this gives the blood-red ferric thiocyanate, $\text{Fe}(\text{SCN})_3$. With ether, which has been freshly distilled or which has been standing over sodium, no such effect is produced.

It appears that various peroxides occur together. H. Wieland proved the presence of dihydroxyethyl peroxide $\text{CH}_3\text{CHOH} \cdot \text{O} \cdot \text{O} \cdot \text{CHOHCH}_3$ which can also be synthesized from acetaldehyde and hydrogen peroxide:



H. King assumes hydroxyethyl hydrogen peroxide $\text{CH}_3\text{CHOH} \cdot \text{O} \cdot \text{OH}$ to be an autoxidation product of ether. According to Rieche the explosive members of these peroxides present in ether are probably ethylidene peroxides



These can be formed from either diethyl peroxide or hydroxyethyl hydrogen peroxide.

Diisopropyl ether $(\text{CH}_3)_2\text{CHOCH}(\text{CH}_3)_2$, which can easily be manufactured industrially by the catalytic addition (BF_3) of *isopropyl* alcohol to propylene, is a knock-resistant motor fuel.

Diisoamyl ether (b.p. $60^\circ\text{--}61^\circ$ at 10 mm) is used as a solvent in Zerewitinoff's method of determining active hydrogen atoms (cf. p. 154). In the pure state it has a pear-like smell.

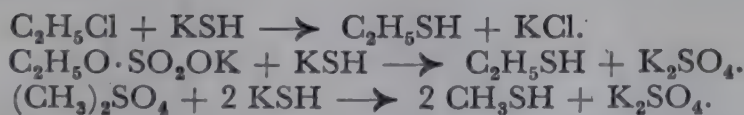
CHAPTER 5

THE MONOVALENT SULPHUR FUNCTION: ALKYL SULPHUR COMPOUNDS

The sulphur analogues of the alcohols and ethers are the *thioalcohols*, $\text{C}_n\text{H}_{2n+1}\text{SH}$, and the *thioethers*, $\text{C}_n\text{H}_{2n+1}\text{SC}_n\text{H}_{2n+1}$. They can be regarded as monoalkyl and dialkyl derivatives respectively of hydrogen sulphide, whose properties they recall in some ways. In chemical properties they show similarities to their oxygen analogues, the alcohols and ethers, but their reactivity, especially towards oxidizing agents, is more diversified.

Thioalcohols, mercaptans. The name *mercaptan* is an abbreviation of the phrase *corpus mercurio aptum*, which was applied to the thioalcohols on account of their ability to form difficultly soluble characteristic mercury salts.

Mercaptans are easily prepared by half alkylating hydrogen sulphide. This is done by heating potassium hydrogen sulphide with any alkylating agent, such as an alkyl halide, alkyl hydrogen sulphate, or dialkyl sulphate. The mercaptans formed are distilled off.



Alcohols can also be converted into thioalcohols by the action of phosphorus trisulphide, P_2S_3 , but the yield is poor and the process is not suitable for the preparation of these substances (Kekulé). The replacement of oxygen by sulphur is better carried out by passing a mixture of hydrogen sulphide and alcohol vapour over thoria heated to $300\text{--}350^\circ$.

The mercaptans are readily volatile substances, the boiling points of the first six members being considerably below those of the corresponding alcohols. The reason for this is that the thioalcohols are less associated than the alcohols. For the same reason, the boiling point of hydrogen sulphide is much lower than that of water, in spite of the fact that the molecular weight of the latter is smaller than that of the former.

	B.p.		B.p.
	H_2S — 61.8°		H_2O + 100°
	CH_3SH + 5.8°		CH_3OH + 64.5°
	$\text{C}_2\text{H}_5\text{SH}$ + 37°		$\text{C}_2\text{H}_5\text{OH}$ + 78°
prim.	$\text{C}_3\text{H}_7\text{SH}$ + 67°	prim.	$\text{C}_3\text{H}_7\text{OH}$ + 97°

			Bp.				Bp.
prim.	norm.	C_4H_9SH	+ 97 ⁰	prim.	norm.	C_4H_9OH	+ 117 ⁰
„	„	$C_5H_{11}SH$	+ 126 ⁰	„	„	$C_5H_{11}OH$	+ 138 ⁰
„	„	$C_6H_{13}SH$	+ 150 ⁰	„	„	$C_6H_{13}OH$	+ 157 ⁰
„	„	$C_7H_{15}SH$	+ 174 ⁰	„	„	$C_7H_{15}OH$	+ 176 ⁰

For the first five mercaptans the difference in the boiling points of two adjacent members is 30°.

The thioalcohols have a penetrating, unpleasant smell, which is so strong that even the smallest amounts can be detected by it. In a perfectly pure state the smell is said to be not so repulsive.

Mercaptans, like hydrogen sulphide, are weak acids. The hydrogen of the —SH group can be substituted by metals. In this way the mercaptides, $C_nH_{2n+1}SM^I$ are formed. They may be compared with the alcoholates as regards constitution. They are, however, more stable than the latter, and are only slightly hydrolysed by water in the cold. The mercaptans, which are insoluble in water therefore dissolve readily — in contrast to the alcohols — in dilute aqueous alkali. The solutions contain the alkali salts $C_nH_{2n+1}SNa$.

The more acid nature of the thioalcohols compared with the alcohols can be understood when it is remembered that hydrogen sulphide itself has a higher hydrogen ion concentration than water.

Amongst the mercaptides, some of those of the heavy metals are characteristic on account of their insolubility and colour. Particularly is this true of the insoluble, colourless mercury salts, which are prepared from mercuric oxide, HgO , or mercuric acetate, $Hg(OCOCH_3)_2$, and mercaptans:



They break down on heating into mercury and a dialkyl disulphide:



The lead mercaptides are yellow:



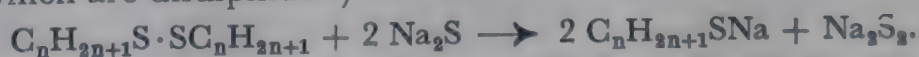
By the action of mild oxidizing agents, and gradually also by the action of atmospheric oxygen, the thioalcohols are oxidized to *dialkyl disulphides*,



These can be regarded as dialkyl derivatives of hydrogen disulphide, and can easily be made by the alkylation of potassium disulphide:



They are liquids, almost insoluble in water, and have repulsive smells. They are reduced (e.g. by sodium sulphide, Na_2S) readily and smoothly to mercaptans. (This reaction is used practically in the bleaching of sulphur dyes (see Ch. 49, section D) which are disulphides.)



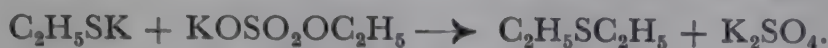
Alkyl disulphides also appear to occur naturally. In garlic oil, the oil which can be distilled in steam from *Allium sativum*, diallyl disulphide, $CH_2=CHCH_2 \cdot S \cdot S \cdot CH_2CH=CH_2$, has been shown to be present (Semmler). Moreover, there is also present (Cavallito) *allicin*, a sulphoxide $CH_2=CHCH_2-SO-S-CH_2CH=CH_2$ derived from diallyl disulphide. Both are degradation products of the alliin (q.v.) which actually occurs in garlic.

A dimercaptal, $CH_2SH \cdot CHSH \cdot CH_2OH$, derived from glycerol, has recently become of practical interest. It is an effective antidote for the war-gas Lewisite ($Cl_2AsCH=CHCl$) and for different metal ions. Commercially it is known as "BAL" (British Anti-Lewisite).

Thioethers. Alkyl sulphides, $(C_nH_{2n+1})_2S$. The *thioethers* are the dialkyl derivatives of hydrogen sulphide. To prepare them, alkali sulphides are heated with alkyl halides or salts of an alkyl hydrogen sulphate:



Obviously, they are also formed from the alkali mercaptides by alkylation:



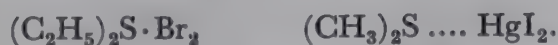
The latter reaction can be used for the preparation of mixed thioethers, $C_nH_{2n+1}SC_mH_{2m+1}$, if the alkyl radical of the mercaptan and that of the alkyl hydrogen sulphate salt are different.

Thioethers are also formed when unsaturated hydrocarbons and mercaptans are exposed to the light of the mercury vapour lamp; thus cetyl-ethyl sulphide is formed from cetene $CH_3(CH_2)_{13}CH=CH_2$ and ethyl mercaptan.

The alkyl sulphides are liquids, insoluble in water, which, when perfectly pure, have a not unpleasant smell. They boil at higher temperatures than the corresponding mercaptans. This is noteworthy because the ethers are, in general, much more volatile than the corresponding alcohols, a phenomenon, as already explained, which is due to the fact that the alcohols are associated while the ethers are not. In the series of sulphur compounds neither the mercaptans, nor the thioethers, are associated to any great extent, and so they show the normal behaviour as far as boiling point is concerned. The thioethers of higher molecular weight are more difficultly volatile than their oxygen analogues, the ordinary ethers.

	B.p.		B.p.		B.p.
$(CH_3)_2S$	+ 38°	$(C_2H_5)_2S$	+ 92°	$(C_3H_7)_2S$	+ 142°
$(CH_3)_2O$	— 23.6°	$(C_2H_5)_2O$	+ 34.6°	$(C_3H_7)_2O$	+ 90.7°

As in the case of the ordinary ethers, which, on account of the unsaturated, basic nature of the oxygen atom, can add on acids and metal salts, so the sulphur atom of the thioethers has a residual affinity, which enables them to add on halogens, alkyl halides, metal salts, etc. These addition products, which, by analogy with the ammonium and oxonium salts are called *sulphonium salts*, must be regarded as similar to these from the point of view of valency, (see also p. 125):

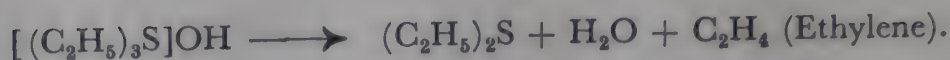


The *sulphonium salts* which are obtained by the addition of alkyl halides to thioethers are specially stable and crystallize well.



They may be formulated as compounds with coordinately trivalent sulphur, and dissociate in water into positive trialkylsulphonium ions $[(CH_3)_3S]^+$ and negative halogen ions. By acting on the halides with moist silver oxide the "sulphonium bases" $[(C_nH_{2n+1})_3S]OH$ are formed. These are compounds which are almost as strong bases as sodium hydroxide. By neutralization with acids any chosen sulphonium salt can be obtained from them. Thus, by the action of hydrogen sulphide, the sulphide $[(C_nH_{2n+1})_3S]_2S$ is obtained. This contains sulphur linked in two different ways. That outside the complex can be split off as an ion, whereas that within the complex cannot be detected by the usual tests for sulphides, unless the molecule is completely destroyed.

The trialkylsulphonium bases are only stable in solution, and decompose, when their solutions are evaporated, according to the equation:



Those sulphonium compounds in which the four groups attached to the sulphur are different can be resolved into optically active isomerides (Pope and Peachey, Smiles).¹ Their molecules are therefore not superimposable with their mirror images. It must be assumed that the three different alkyl radicals and the sulphur atom can be linked together in a stable, asymmetrical arrangement (three-sided pyramid), and that the free positive charge on the central sulphur atom acts in a way as a fourth bond, stabilizing the system. The following are examples of sulphonium compounds which have been resolved:

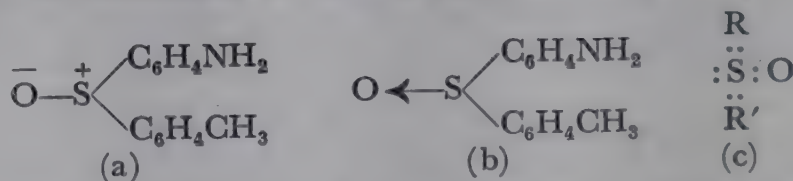


The even more interesting observation from the stereochemical point of view that the sulfoxides (see below), e.g.



and the esters of the sulphinic acids $\left(\text{e.g. } \text{CH}_3 \cdot \text{C}_6\text{H}_4 \cdot \text{S} \begin{array}{l} \nearrow \text{O} \\ \searrow \text{OC}_2\text{H}_5 \end{array} \right)$ could be

resolved into optically active forms, shows that an arrangement of only three groups and a central atom can be asymmetric (J. Kenyon and H. Philips). The fourth valency bond of the sulphur, which, in the sulphonium salts $[\text{R}_3\text{S}]\text{X}$ is used for the linking of the negative ion, has, in the case of the sulfoxides, and sulphinic esters, been linked to the oxygen atom, and has retained its special nature. It is noteworthy that the two valencies linking the oxygen are not equivalent (one is polar, the other non-polar). In such a case, the bond is referred to as a semi-polar bond, and the formula is written as (a), (see also p. 125):



The sulphur atom in sulfoxides and sulphinic esters is linked with three different groups and an electron pair (c). It is in the same steric relationship as an asymmetric C-atom, the lone electron pair occupying a corner of a tetrahedron.

The determination of the so-called "parachor" is a useful method of detecting the presence of a semipolar bond. This molecular constant, introduced by Sugden, is given by the expression

$$P = \frac{M}{D} \gamma^{1/4}$$

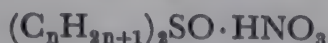
and is almost independent of temperature. (M/D = molecular volume, γ = surface tension).

The value of the parachor can be calculated additively from the atomic parachors, and the values for the various linkings. Multiple links cause an increase

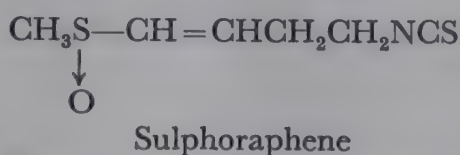
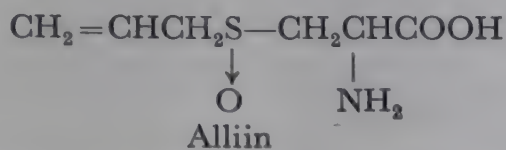
¹ See M. SCHOLTZ, *Die optisch aktiven Verbindungen des Schwefels, Selen, Zinns, Siliciums und Stickstoffs*, Stuttgart, (1906), and also text-books on Stereochemistry. — CH. SUTER, *The Organic Chemistry of Sulfur*, New York and London, (1945).

in the value of the parachor. This is independent of the type of atom linked, being the same for the linkages in $C=C$, $C=O$, $N=N$, $N=O$, etc. It amounts to 23.2 units for the double bond, and 46.6 units for the triple bond. On the other hand, the semipolar double bonds do not cause analogous exaltations, and can thus be detected. This test shows the existence of the semipolar double bond in the sulphinic acids and sulfoxides.

Sulphoxides and sulphones. The *dialkyl sulfoxides*, $(C_nH_{2n+1})_2SO$, are produced, for example, by the action of benzoyl hydroperoxide or H_2O_2 on thioethers, or in the form of their nitrates



when the thioethers are oxidized by nitric acid. They are unstable, weakly basic, substances, which are easily reduced again to *dialkyl sulphides*. Recently, two sulphoxides have been found in plants, *alliin* in garlic (*Allium sativum* L.) (A. Stoll and E. Seebeck), and *sulphoraphene* in radish seeds (*Raphanus sativus*) (H. Schmid and P. Karrer). Both substances are, with respect to the sulfoxide group, sterically homogeneous, i.e. asymmetric.

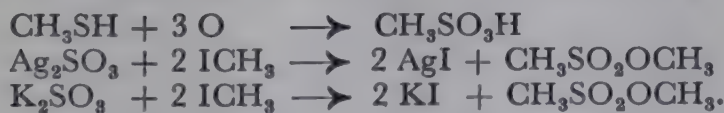


The sulphones $(C_nH_{2n+1})_2 \cdot SO_2$ are more stable and are obtained from the thioethers (or sulfoxides) by stronger oxidation with potassium permanganate or nitric acid. They are neutral, odourless substances, which crystallize well, and are very stable towards reducing agents. Dimethyl sulphone has been found in the blood and suprarenal glands of animals. The group of the *sulphonals*, important therapeutically, belongs to the disulphones (see p. 179).

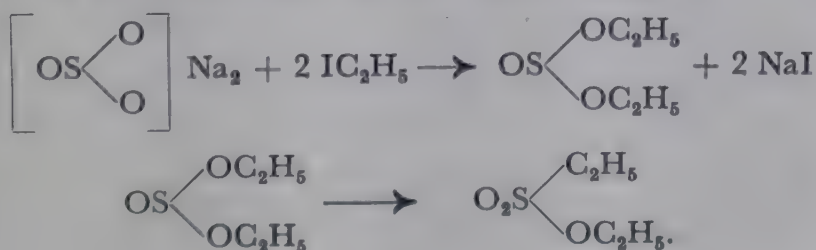
Alkylsulphonic acids. The alkylsulphonic acids are more difficult to obtain than their analogues of the benzene series. This is the chief reason why they are not so important as the latter. Some of the alkylsulphonic acids are obtained from paraffins by sulphonation, i.e. by direct reaction with sulphuric acid, but the reaction does not proceed smoothly, and appears to be limited to a few hydrocarbons.



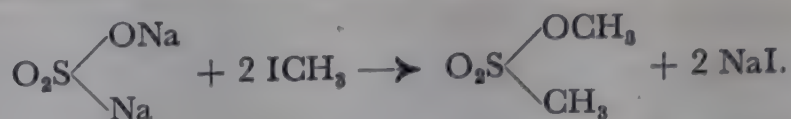
The alkylsulphonic acids can be obtained more easily from mercaptans by oxidation (with nitric acid), or by the alkylation of sulphites. In the latter case, excess of the alkylating agent gives esters of the sulphonic acids:



The alkylation of sulphites does not lead to the formation of esters of sulphurous acid, but of alkylsulphonic acids. This may be explained by the fact that dialkyl sulphites and alkyl hydrogen sulphites rearrange easily into alkylsulphonic acids. Potassium iodide is a suitable agent for this rearrangement:



It can also be assumed that the sulphite reacts as the unsymmetrical form:



From this uncertainty it may be said that in this and similar cases, *conclusions concerning the constitution of metal salts cannot be drawn from the known constitutions of organic compounds produced from them by alkylation.*

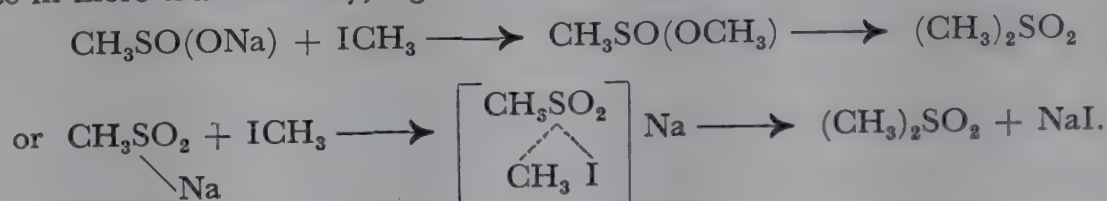
The alkylsulphonic acids are strong acids, easily soluble in water, and hygroscopic. Their salts crystallize well. They are very resistant to the action of acids and alkalis. By the action of phosphorus pentachloride they are converted into the alkylsulphonyl chlorides $\text{C}_n\text{H}_{2n+1}\cdot\text{SO}_2\text{Cl}$

which give *sulphinic acids*, $\text{C}_n\text{H}_{2n+1}\text{SO}_2\text{H}$, or mercaptans on reduction. These reactions provide, at the same time, a proof of the constitution of the sulphonic acids, since they show that both the alkyl radical and the hydroxyl group must be attached to the sulphur.

Aliphatic sulphonyl chlorides have also been obtained by irradiating a mixture of paraffins, SO_2 , and chlorine with ultra-violet light:



Alkylation of the salts of the sulphinic acids gives sulphones. This process is, however, not a conclusive proof of the structure of the salts of the sulphinic acids, since it can take place in more than one way, e.g.:



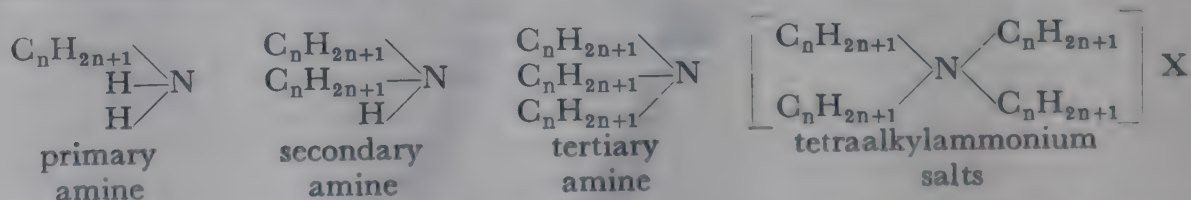
CHAPTER 6

MONOVALENT NITROGEN FUNCTIONS

I. Amines

The *aliphatic amines*, discovered by Wurtz, are the alkyl derivatives of ammonia. Their simplest method of preparation — the alkylation of ammonia — already points to this formulation, which is confirmed by all other reactions of the amines.

According to the number of hydrogen atoms of the ammonia which are substituted by alkyl groups, the amines are called primary, secondary, and tertiary amines; the tetraalkylammonium salts may be regarded as completely alkylated ammonium salts, derived from the corresponding quaternary ammonium bases.

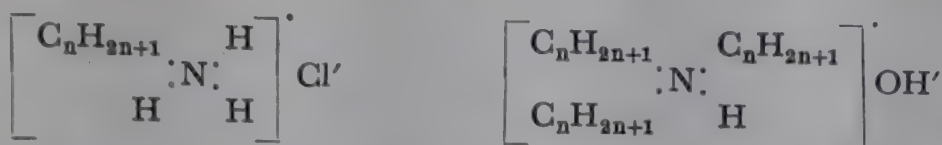


The aliphatic amines are, like ammonia, bases, but they ionize in aqueous solution to a greater extent than the latter, and are therefore stronger bases.

The salts and hydroxides of the organic amines were formerly written with pentavalent nitrogen as shown by the formulæ:

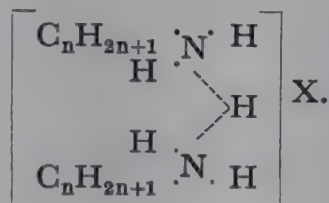


It is, however, convenient to regard them, according to A. Werner¹, like the inorganic ammonium salts, as coordination compounds, and to distinguish between the ammonium ion (with coordinately tetravalent nitrogen) and the negative acid, or hydroxyl, ion:



According to this view the alkyl radicals and hydrogen atoms are directly linked with the nitrogen of the alkylammonium salt, in the inner sphere. This is no doubt the case for the tetraalkylammonium salts. The acid radical or the hydroxyl group, on the other hand, are linked, outside the complex, agreeing with the fact that the alkylammonium salts break down in aqueous solution into substituted ammonium ions and acid ions.

The coordination formula for the alkylammonium salts has the advantage over that involving pentavalent nitrogen in that it gives a straightforward explanation of the existence of addition compounds of alkylamines and metal salts, and of the occurrence of the so-called "abnormal" ammonium salts, in which the ratio of amine to acid is other than 1:1, e.g.:



Moreover, it is the only formula which is in harmony with the current concepts of the electronic nature of chemical valency (see the following paragraphs on "onium compounds").

Different types of isomerism which can occur with the amines cause this class of compounds to be a very large one. Besides the isomerism due to the different branching of the carbon chain, there is another type due to the different position which the NH_2 group can take up in the hydrocarbon radical, and a third type in which a compound of one given empirical formula can exist as a primary, secondary, or tertiary amine (*metamerism*).

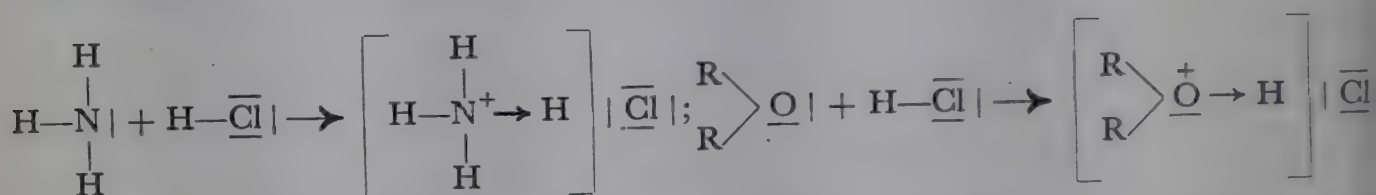
ELECTRONIC FORMULATION OF THE "ONIUM COMPOUNDS" AND RELATED SUBSTANCES. As stated earlier (p. 62) it has become customary in the "electronic formulation" of organic compounds to represent an electron pair by a dash, and a so-called lone pair, which is attached to only one atomic nucleus, by a horizontal or vertical dash as shown below. In the following three electronic formulæ there are lone electron pairs on the oxygen atom of the ether, and on the nitrogen atom of the ammonia:

¹ Cf. A. WERNER, *Neuere Anschauungen auf dem Gebiete der anorganischen Chemie*, 4th ed., Brunswick (1920); and the new edition of the same work revised by P. Pfeiffer.

	Structural formula	Electronic formula	Schematic electronic formula
Ether	$R-O-R$	$R : \ddot{O} : R$	$R-\overline{\text{O}}-R$
Ammonia	$\begin{array}{c} H-N-H \\ \\ H \end{array}$	$\begin{array}{c} H : \ddot{N} : H \\ \ddot{H} \end{array}$	$\begin{array}{c} H-\overline{N}-H \\ \\ H \end{array}$
Methane	$\begin{array}{c} H \\ \\ H-C-H \\ \\ H \end{array}$	$\begin{array}{c} H \\ \vdots \\ H : C : H \\ \vdots \\ H \end{array}$	$\begin{array}{c} H \\ \\ H-C-H \\ \\ H \end{array}$

Compounds which possess lone pairs of electrons are capable of forming compounds of a higher order, which were called by A. Werner coordination compounds. All the so-called onium compounds (ammonium, oxonium, sulphonium salts, and similar compounds, see p. 117 and 121) belong to this class. In these compounds the central atom utilizes one more linkage than corresponds to its normal valency; its *coordination valency* is thus one unit greater than the normal valency.

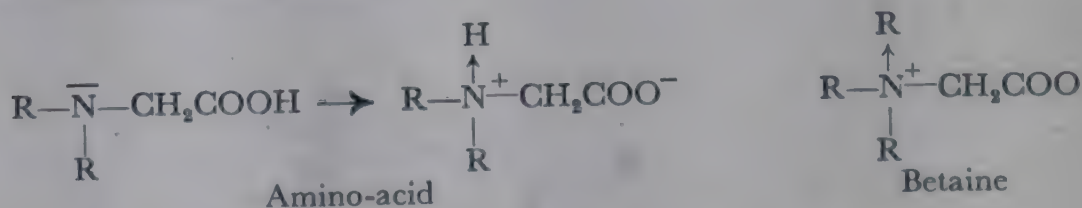
The formation of such onium compounds may be represented electronically by the following formulæ:



In the formation of these complex salts (ammonium and oxonium compounds) the electrochemical valency of the nitrogen and the oxygen undergoes no change; there is, however, a change in the function of electron pairs. The proton of the hydrogen chloride breaks its link with the chlorine ion and enters the electron system of the nitrogen or oxygen. In this way the resulting complex ammonium or oxonium group acquires one positive charge.

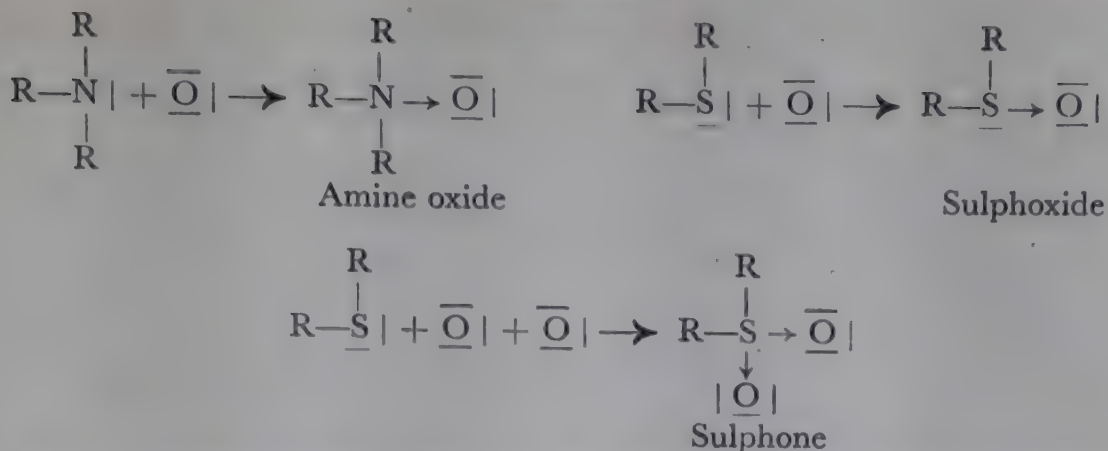
In the ammonium, oxonium, and sulphonium ion complexes the groups coordinated with the central atom are all linked to it in the same way, viz. by an electron pair. While, however, in the ammonia and ether molecules the bonds linking the central atom with the others are made up of two electrons, one supplied by the central atom and the other by the linked atom, in the ammonium and oxonium complexes the central atom supplies both electrons for the linking of the newly entering proton. The coordination centre in the latter cases is thus an electron donor, which is represented in the formulæ by an arrow indicating in which direction the electrons are transferred.

Ammonium salt formation can also take place intramolecularly (as for example in the amino-acids, p. 285). This process can be represented electronically in a similar way as for the simple ammonium salts:

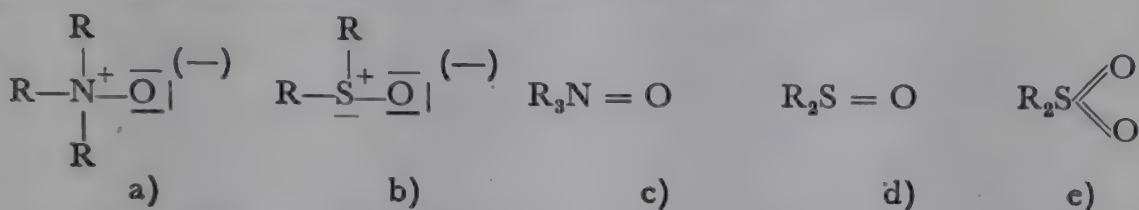


This formulation can be similarly applied to the betaines (p. 296).

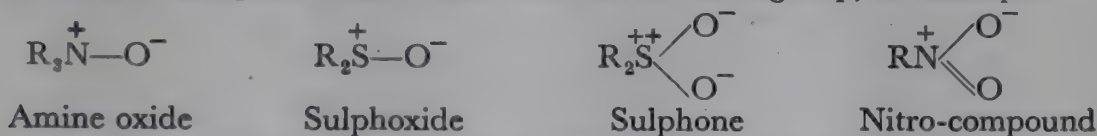
In the formation of amine oxides, sulfoxides, sulphones, and similar substances, analogous processes occur as in the formation of ammonium salts. Thus in the formation of an amine oxide the lone pair of the nitrogen enters the oxygen sextet. Similarly with the sulfoxides and sulphones, lone pairs of the sulphur play a like part:



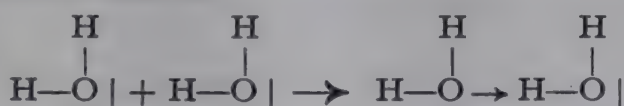
The link between nitrogen and oxygen in the amine oxides, and between sulphur and oxygen in the sulfoxides and sulphones is thus always effected by a single electron pair, which in the classical theory of valency corresponds to a single bond. The nitrogen in the amine oxides, and the sulphur in the sulfoxides have, however, simultaneously acquired a positive charge, and the oxygen a negative charge (a and b).



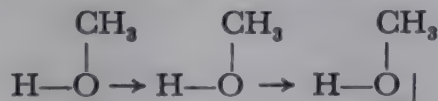
When the classical theory of valency puts a double bond between N or S and O in the amine oxides, sulfoxides, and sulphones (formulae c, d, and e), this must, therefore, be interpreted as meaning that only one of the bonds stands for the usual electron pair bond, whilst the other expresses the ionic state of the molecule. Such a bond is called a *semipolar* (or dative) bond. A semipolar bond is also found in the nitro-group, for example:



The association and polymerization phenomena, which occur in general with hydroxyl compounds, are analogous to onium salt formation. Thus, the association of water can be explained as the joining of a hydrogen atom of one water molecule to a lone pair of the oxygen atom of another molecule:



Consequently, the associated alcohols can be represented symbolically as follows:



and the formulae a) and b) may be written to represent the dimolecular carboxylic acids; these formulae correspond to mesomeric states:



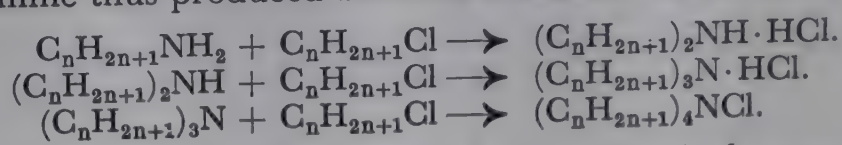
In all these associated compounds with hydroxyl groups there are *hydrogen bonds* (or *hydrogen bridges*). The hydrogen here has a coordinate valency of two.

Owing to the tendency of the hydrogen of the OH-group to enter the electron system of an atom which has a lone pair, intramolecular hydrogen bonds are also often formed. These are of considerable importance in connection with the physical and chemical properties of the compounds concerned (see, for example, the formation of "chelate" compounds, Ch. 47).

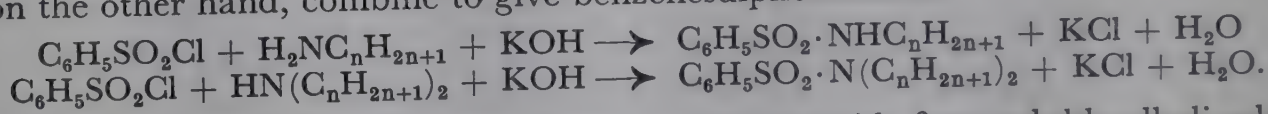
Methods of preparation. 1. According to a process discovered by A. W. Hofmann, *primary, secondary, tertiary, and quaternary* amines are formed together if some alkylating agent, such as an alkyl halide, alkyl nitrate, or dialkyl sulphate acts on aqueous or alcoholic solutions of ammonia. This "alkylation of ammonia" is theoretically the simplest method of preparing the amines. Practically, however, its use is limited, because in most cases it is almost impossible to stop the alkylation at a definite stage below the quaternary ammonium compound, and the separation of the different reaction products presents great difficulties. The first stage of the reaction leads to the formation of a salt of the monoalkylamine:

$$\text{C}_n\text{H}_{2n+1}\cdot\text{Cl} + \text{NH}_3 \longrightarrow \text{C}_n\text{H}_{2n+1}\text{NH}_2\cdot\text{HCl}.$$

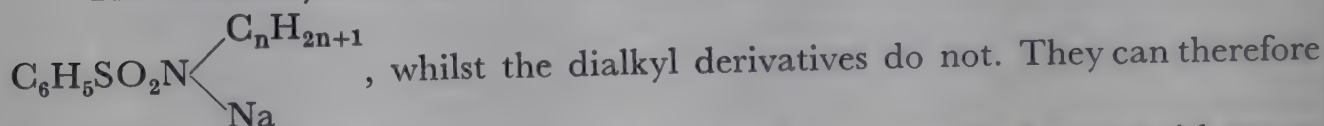
This salt, however, partially reacts with the excess of ammonia present, and the free primary amine thus produced becomes available for further alkylation:



The quaternary ammonium salts can be quantitatively separated from the primary, secondary, and tertiary amines by making use of the fact that they are stable to caustic alkalis. The mixture of the different amine salts is made alkaline with caustic soda, and distilled in steam. The quaternary ammonium compound remains behind in the flask, whilst primary, secondary, and tertiary amines distil over. Their separation is not easy, and the same methods cannot always be used. In many cases it can be successfully accomplished by means of benzenesulphonyl chloride (or toluenesulphonyl chloride). Tertiary amines in aqueous alkaline solution are unaffected by this reagent. Primary and secondary amines, on the other hand, combine to give benzenesulphonamides:



The monoalkyl derivatives of benzenesulphonamide form soluble alkali salts,

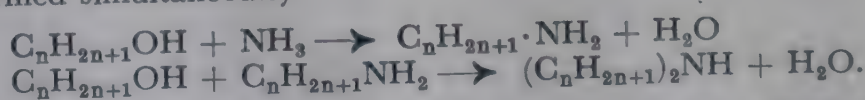


be separated, and both sulphonamides are then decomposed by heating with strong hydrochloric or sulphuric acid:



In certain cases this process of separation is, however, unreliable owing to the occurrence of side-reactions, and must be modified.

2. V. Merz has prepared amines from *alcohols by heating them with zinc ammine chloride*. The yields obtained by this process are usually small, and primary, secondary, and tertiary amines are formed simultaneously:



3. Primary amines are readily formed by the *alkaline hydrolysis of isocyanate esters*. It was in this way that they were discovered by Wurtz who recognized that they differed from ammonia in being inflammable.



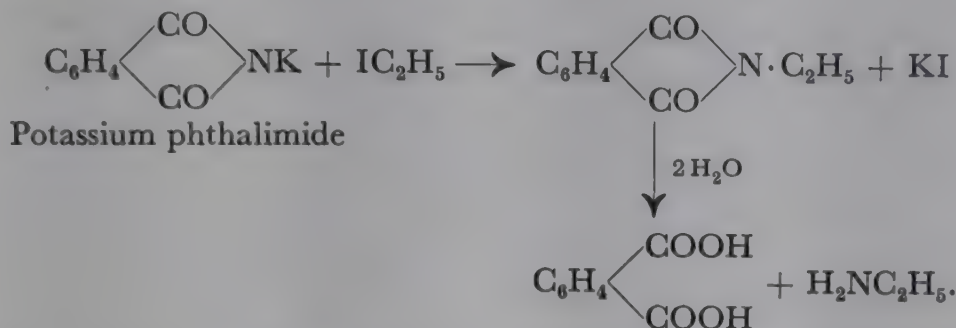
4. *Aliphatic nitro-compounds yield amines on reduction*. The reaction goes smoothly

with the most diverse reducing agents (ammonium sulphide, tin and hydrochloric acid, hydrogen and platinum, etc.):



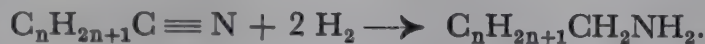
This method, due to Zinin, is of greater importance in the aromatic series than in aliphatic chemistry, since the aliphatic nitro-compounds are much more difficult to obtain than the aromatic ones. (They are prepared from alkyl halides and metal nitrites, alkyl nitrites being always formed as by-products).

5. Gabriel's method may be used for the preparation of primary amines. It is based on the reaction between *potassium phthalimide* and the *alkyl halides*. The phthalic acid radical is removed from the compound produced by boiling with acid:

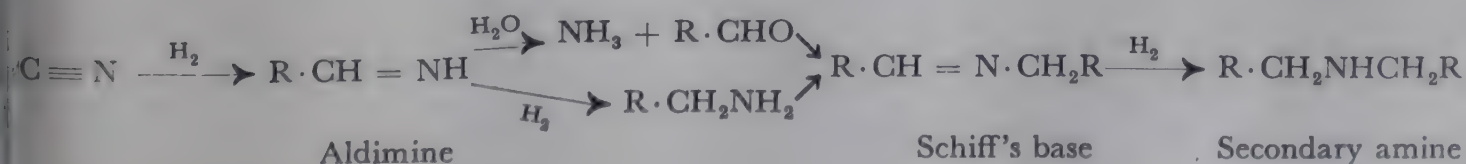


As potassium phthalimide is easily prepared, Gabriel's method is often used in modern preparative chemistry.

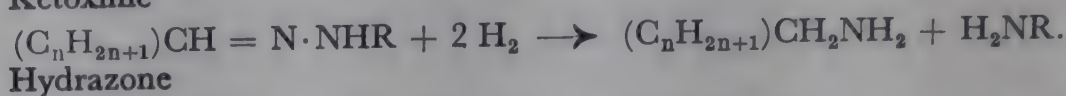
6. The *reduction of nitriles* (alkyl cyanides, $\text{C}_n\text{H}_{2n+1} \cdot \text{C} \equiv \text{N}$) gives rise to amines, but certain irregularities have been observed. By the older Mendius method, using tin and hydrochloric acid as the reducing agent, primary amines are formed, but in small yield:



The reduction is better carried out by sodium and alcohol, and in this form the reaction has proved of great service in the hands of Krafft, for the synthesis of higher amines of the aliphatic series. More recently the catalytic reduction of nitriles with hydrogen in the presence of nickel, or hydrogen and platinum and palladium respectively, has been thoroughly investigated (Sabatier and Senderens, Rupe, and others). It has been shown that primary or secondary amines, or mixtures of the two, result according to the nature of the nitrile. Whilst the formation of a primary amine can easily be accounted for, it is more difficult to see how a secondary amine can be produced. Apparently the reaction proceeds in such a way that the nitrile is converted into an aldimine by the addition of a molecule of hydrogen, and this is then partly hydrolytically decomposed to an aldehyde, and partly reduced to a primary amine. The two latter substances combine to form what is known as a Schiff's base, and this is finally converted into a secondary amine by the addition of hydrogen; or the aldimine reacts directly with a molecule of the primary amine formed with production of a Schiff's base:



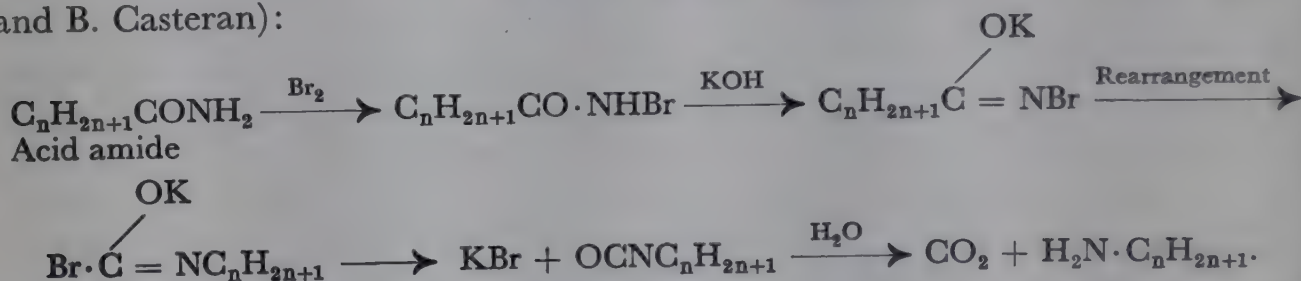
7. *Oximes* and *hydrazones*, which are easily obtainable from aldehydes and ketones, can often be readily reduced electrolytically, or with sodium amalgam and acetic acid, aluminium amalgam, or hydrogen and a catalyst, to give amines:



This process thus affords a way for the conversion of aldehydes and ketones into amines.

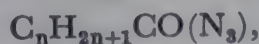
8. Methods of obtaining *amines from carboxylic acids* are of great importance from the preparative point of view. Different, and very useful methods are available. The first is the *Hofmann degradation of acid amides*, the second the *Curtius degradation of acid azides*, and the third the reduction of acid amides with LiAlH_4 .

Acid amides are oxidized by treatment with bromine (or chlorine) and alkali (hypobromite). The reaction proceeds through various intermediate stages. First a monobromoamide is formed, which then rearranges to give probably an isocyanate. The latter is then hydrolysed by the alkali present in the solution with the formation of an amine and carbon dioxide, as shown above. If the amide of an α -trisubstituted acid, e.g. dimethylpropylacetamide, $\text{C}(\text{CH}_3)_2(\text{C}_3\text{H}_7)\text{CONH}_2$, is used in this reaction, the isocyanates produced, R_3CNCNCO , are considerably more stable with respect to alkali, and can be isolated without difficulty (M. Montagne and B. Casteran):

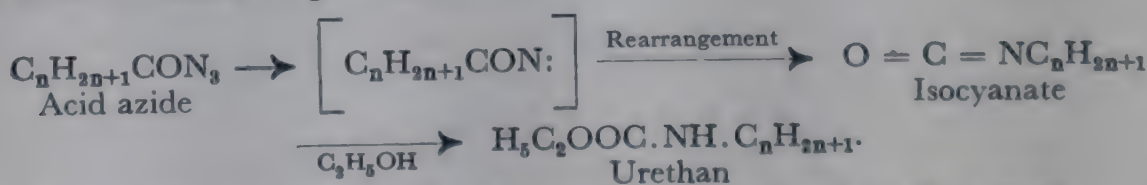


The reaction is carried out practically by mixing 1 gm-mol. of the amide with 1 gm-mol. of bromine, adding at least 4 gm-mols. or an excess of alkali, and warming. In a short time the formation of the amine is complete. For the mechanism of the reaction in the case of the amides of α -hydroxycarboxylic acids, see p. 263.

In the Curtius process of obtaining amines from the *acid azides*,



intramolecular rearrangements also occur. If the acid azide is warmed in alcohol, one molecule of nitrogen is first split off. The unstable radical thus formed rearranges to an isocyanate, which immediately takes up alcohol, forming a so-called urethan, an ester of an alkylcarbamic acid. The urethans are hydrolysed on heating with acids or alkalis to give amines:



The two methods just described allow the conversion of an acid amide into an amine containing one carbon atom less. It has, however, been possible to

prepare amines with the same number of carbon atoms as the amides from which they are obtained, by direct reduction with LiAlH_4 (E. Schlittler). By means of this procedure, the carboxyl group is thus changed via the amide into the grouping $-\text{CH}_2\text{NR}_2$:

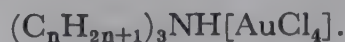


In the case of optically active carboxylic acids, in which the carbonyl group is attached to an asymmetric carbon atom (e.g. $[\text{C}_6\text{H}_5\text{CH}_2]\text{CH}_3\text{CHCOOH}$), both the Hofmann amide reaction and the Curtius azide reaction give rise to optically active amines (Jones and Wallis). The group $[\text{C}_6\text{H}_5\text{CH}_2]\text{CH}_3\text{CH}-$, which wanders from C to N in the intermediate product $[\text{C}_6\text{H}_5\text{CH}_2]\text{CH}_3\text{CHCON} <$ retains its configuration during the process.

Properties of amines. The first two aliphatic amines are gases at ordinary temperatures, the middle members are liquids, and the highest solids. The solubility in water decreases with increasing molecular weight. The first few members are very soluble. The smell of the lower amines recalls that of ammonia, but is characteristically different and less pungent. The solid amines are almost, if not quite, odourless.

		b.p.			b.p.	m.p.
	CH_3NH_2	— 6.7°	norm.	prim.	$\text{C}_8\text{H}_{17}\text{NH}_2$	179°
	$\text{C}_2\text{H}_5\text{NH}_2$	+ 19°	"	"	$\text{C}_9\text{H}_{19}\text{NH}_2$	195°
prim.	$\text{C}_3\text{H}_7\text{NH}_2$	+ 49°	"	"	$\text{C}_{10}\text{H}_{21}\text{NH}_2$	217° + 17°
norm.	$\text{C}_4\text{H}_9\text{NH}_2$	+ 77.8°	"	"	$\text{C}_{11}\text{H}_{23}\text{NH}_2$	233° + 16.5°
"	$\text{C}_5\text{H}_{11}\text{NH}_2$	+ 104°	"	"	$\text{C}_{12}\text{H}_{25}\text{NH}_2$	248° + 27°
"	$\text{C}_6\text{H}_{13}\text{NH}_2$	+ 129°	"	"	$\text{C}_{13}\text{H}_{27}\text{NH}_2$	265° + 27°
"	$\text{C}_7\text{H}_{15}\text{NH}_2$	+ 153°				

The amines combine with acids to give well-crystallized salts, which are soluble in water. The picrates (or picrolonates, or styphnates) of the amines are characteristic. They usually crystallize well and have sharp melting points. The salts of the amines combine with many metal salts giving double salts. Those with gold chloride or platinic chloride often serve for the characterization of the bases:



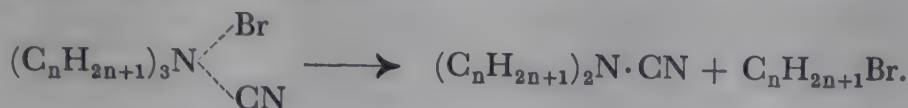
In the alkylammonium salts, the ammonium ion plays the same part as the sodium ion in sodium chloride. It can therefore be predicted that free ammonium and its alkyl derivatives would possess similar chemical properties to an alkali metal, and experiments have already been carried out in the past (Moissan) to isolate free ammonium radicals. In more recent times, Schlubach has shown that tetraethylammonium, $(\text{C}_2\text{H}_5)_4\text{N}$, can be obtained in liquid ammonia solution by electrolysis of the strongly cooled solution of tetraethylammonium iodide in liquid ammonia, or by the action of lithium dissolved in liquid ammonia on tetraethylammonium chloride:



The tetraethylammonium was not isolated in the free state, as it decomposes at the boiling point of liquid ammonia. Its existence in solution however, could be recognized by a number of reactions. With iodine tetraethylammonium iodide is formed, with sulphur the corresponding sulphide; like metallic potassium, tetraethylammonium combines with dimethylpyrone (Ch. 61) and triphenylmethyl (see p. 400) to form red compounds. It appears to exist in a blue and a colourless form.

The different behaviour of the primary, secondary, and tertiary amines towards nitrous acid can be used to distinguish between them. *Primary amines* react with nitrous acid to form *primary alcohols*. Intermediate products in this reaction are probably the monoalkylamides of nitrous acid (a), which are unstable in the aliphatic series, and the equally unstable diazonium hydroxides (b) arising from the latter by rearrangement:

Another method of de-alkylating tertiary amines depends on the fact that the addition compounds of tertiary amines with cyanogen bromide are easily decomposed on heating into a dialkylcyanamide and alkyl halide (v. Braun). As a rule the smallest alkyl radical is split off as the alkyl halide:



METHYLAMINE, CH_3NH_2 , occurs in *Mercurialis annua* and *perennis*, and is produced largely by the decomposition of alkaloids and proteins.

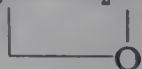
DIMETHYLAMINE and TRIMETHYLAMINE can be detected in herring brine. *Dimethylamine* can easily be obtained in a state of purity by heating nitrosodimethylaniline (Ch. 31) with concentrated alkali:



TRIMETHYLAMINE is formed if ammonium salts are methylated by heating with formaldehyde under pressure:



It is also obtained from beet-sugar molasses wash by decomposition of the betaine, $(\text{CH}_3)_3\text{N}\cdot\text{CH}_2\text{CO}$, contained therein. Trimethylamine also occurs in various plants.



The odour of trimethylamine, especially when greatly diluted, is very repulsive, being fish-like, and adhering tenaciously to clothes. In the concentrated state, the base smells somewhat like ammonia.

TETRAMETHYLAMMONIUM HYDROXIDE, $(\text{CH}_3)_4\text{N}\cdot\text{OH}$. Tetramethylammonium salts are very easily formed by the exhaustive methylation of ammonia, or by the addition of a methyl halide to tertiary amines. A solution of tetramethylammonium hydroxide is obtained from the halogen salts by treatment with moist silver oxide:



On careful evaporation of the water, a crystalline residue, consisting of various hydrates of tetramethylammonium hydroxide remains.

This is a very strong base, comparable in strength to the alkali bases. With acids it gives tetramethylammonium salts and water. Tetraalkylammonium bases are unstable to heat; the tetramethyl compound breaks down on heating into the tertiary amine and methyl alcohol:

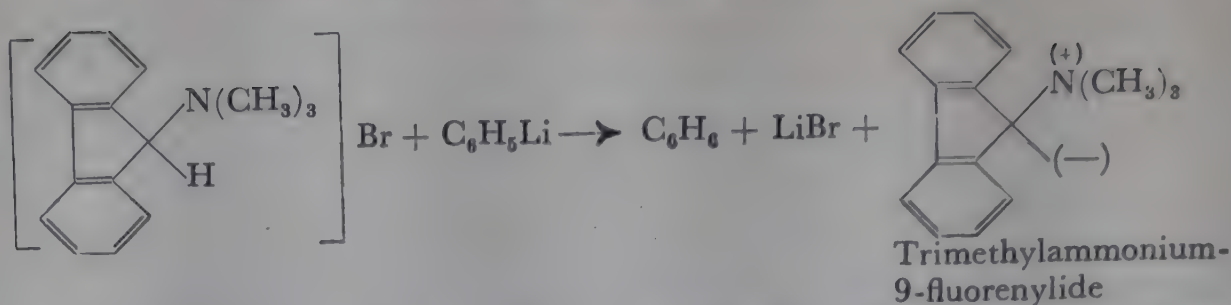


Other quaternary ammonium bases containing hydrogen in the β -position relative to nitrogen usually decompose in a somewhat different way in this process, viz. into a tertiary amine, olefin, and water:



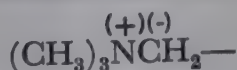
This important method of breaking down quaternary ammonium compounds, discovered by A. W. Hofmann, has played a prominent part in the investigation of alkaloids and other nitrogen compounds.

In recent times it has proved possible to make "internal" ammonium salts in which a negatively charged carbon group takes the part of the anion (G. Wittig). Such a salt is formed by the action of phenyllithium on 9-fluorenyl-trimethyl-ammonium bromide:



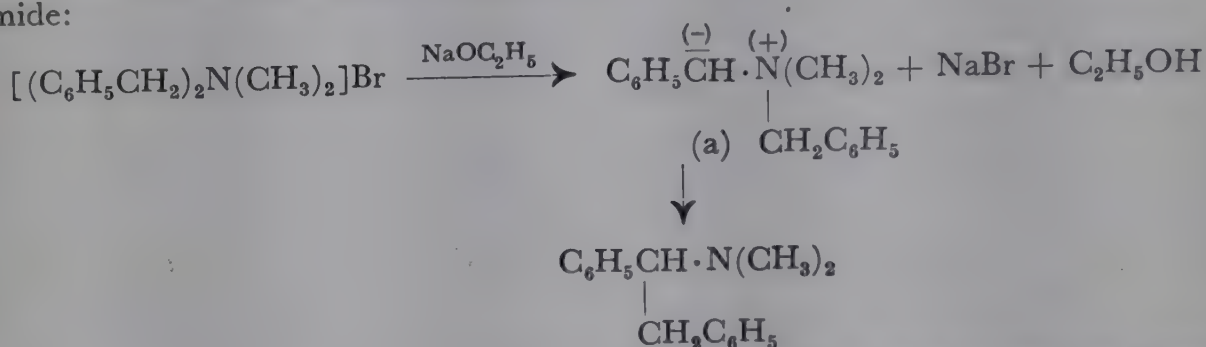
This interesting compound is ochre-yellow in colour and dissolves in water, forming 9-fluorenyl-trimethyl-ammonium hydroxide, and adds on alkyl halides, e.g. CH_3I , forming (9-methyl-fluorenyl)-9-trimethylammonium iodide.

A still simpler example of an "internal" ammonium salt is trimethylammonium methylyde, which is obtained from tetramethylammonium chloride and phenyl lithium



With iodine it affords iodomethyl-trimethyl-ammoniumiodide $[(\text{CH}_3)_3\text{NCH}_2\text{I}]\text{I}$, and with methyl iodide it gives ethyl-trimethyl-ammonium iodide.

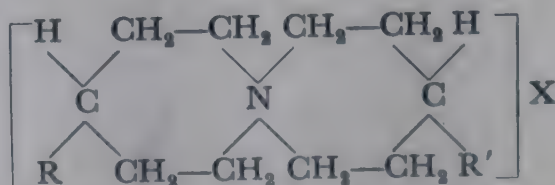
These "internal" ammonium salts may also be looked upon as intermediate products of the so-called Stevens rearrangement, which takes place under the action of sodium alcoholate on certain quaternary ammonium salts such as dimethyl-dibenzyl-ammonium bromide:



The unstable internal ammonium salt (a), or betaine, seeks to be stabilized through rearrangement. A prime condition for the rearrangement to take place is a mobile hydrogen atom in an alkyl group of the ammonium salt, which is split off as a proton by the alcoholate.

Quaternary ammonium salts in which all four alkyl radicals are different can be resolved into optically active forms. This was first shown by Le Bel for methyl-ethyl-propyl-isobutyl-ammonium chloride. This compound exists in two forms, an α - and a β -modification. *Penicillium glaucum* destroys the dextrorotatory form of the first, and the lævorotatory form of the second. Later, various other investigators have obtained other optically active ammonium salts (e.g. benzyl-phenyl-allyl-methyl-ammonium compounds). As regards the stereochemical structure of these nitrogen compounds¹, the obvious assumption is made that the four different alkyl radicals are grouped tetrahedrally round the nitrogen, so that, stereochemically, the ammonium salts are built up in a similar way to carbon compounds.

The fact, discovered by Mills and Warren, that cyclic ammonium salts of the formula



may be obtained in enantiostereoisomeric forms, also supports this view. Such

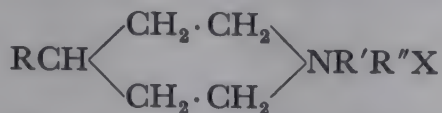
¹ G. E. WEDEKIND, *Die Entwicklung der Stereochemie des fünfwertigen Stickstoffs im letzten Jahrzehnt*, Stuttgart, (1909). Also text-books on stereochemistry.

molecules, however, have an unsymmetrical structure only if the two rings are arranged tetrahedrally about the nitrogen atom (cf. the analogous relations with the allene derivatives, Ch. 54, carboxylic acids). Plane or pyramidal models for the molecules of these substances would not make them optically active.

Quaternary ammonium salts of 4-phenyl- and 4-hydroxyphenyl-piperidine occur in geometrically isomeric forms if R' and R'' are different. If they are the same, only one form is found:

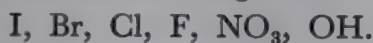


These facts can only be explained by assuming a tetrahedral arrangement of substituents about the nitrogen. If the arrangement were pyramidal, all quaternary piperidinium salts substituted in the 4-position

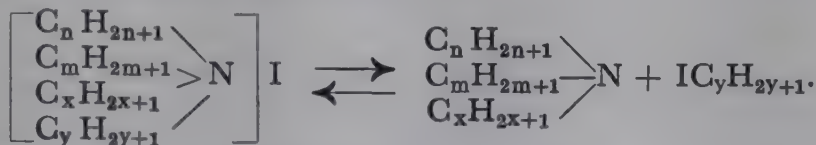


should occur in two geometrically isomeric forms, even if the radicals R' and R'' linked to the nitrogen are identical.

The rapid racemization which optically active ammonium salts undergo in solution is remarkable. It proceeds most rapidly for the iodides, and slowest for the hydroxides. For other ions the rapidity is usually in the following order:



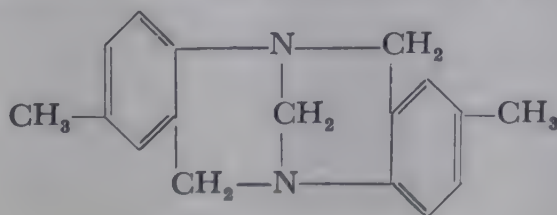
Possibly the rapid racemization of optically active quaternary ammonium salts is due to the fact that, in solution, they are in dynamic equilibrium with their products of dissociation, the tertiary amine and alkyl halide:



The re-addition of the alkyl halide to the tertiary amine must obviously lead to an inactive product, since the conditions for the formation of the two enantiostereoisomers are equally favourable (E. Wedekind).

However, optically active ammonium salts (e.g. N-methyl-allyl-tetrahydroquinolinium salts) also appear to exist, in which the racemization is a true auto-racemization, similar to that of carbon compounds.

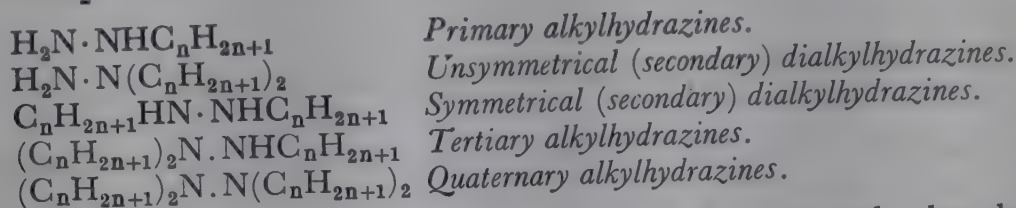
V. Prelog succeeded in resolving a compound with asymmetric *trivalent* nitrogen atoms into optically active forms. The failure of numerous previous attempts in this respect can be explained on the assumption, that in such tertiary amines the substituents grouped around the nitrogen swing through the plane of the substituents, so that sterically homogeneous forms cannot be obtained. This difficulty has been avoided by choosing a substance with trivalent nitrogen atoms, the substituents of which form part of ring systems and are, therefore, prevented from swinging through a plane. Such a tertiary amine is the so-called Tröger base:



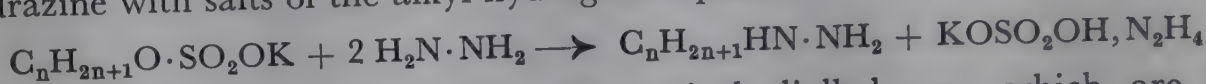
which has actually been obtained in optically active forms (highest rotation observed, $[\alpha]_D^{17} = +75^\circ$).

II. Alkyl derivatives of hydrazine

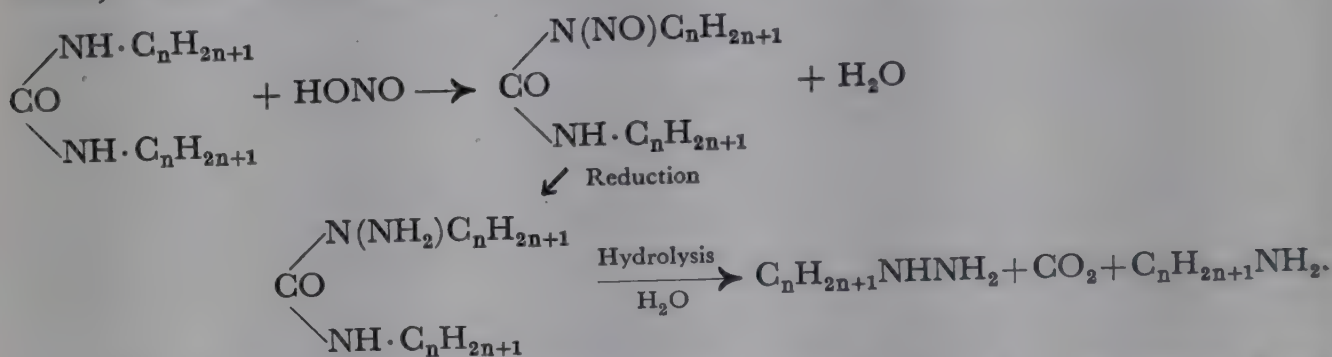
The following series of alkyl compounds are derived from hydrazine, $\text{H}_2\text{N}\cdot\text{NH}_2$:



The primary *alkylhydrazines* are obtained, for example, by the alkylation of hydrazine with salts of the alkyl hydrogen sulphates:



They can also be obtained from symmetrical dialkylureas, which are first converted into nitroso-compounds. These are then reduced to hydrazine derivatives, which are hydrolysed by mineral acids to the primary alkylhydrazines:



The monoalkylhydrazines are strong bases, fuming in air. They form well-crystallized salts. Like hydrazine itself they are strong reducing agents.

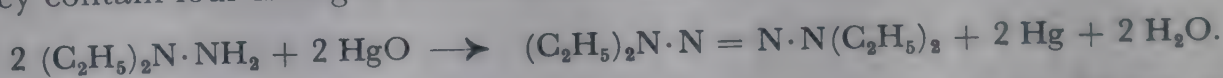
The *unsymmetrical dialkylhydrazines* are obtained, for example, from secondary amines through their nitroso-derivatives:



They too are strong bases, which easily add on one molecule of an alkyl halide to give trialkylhydrazonium salts:

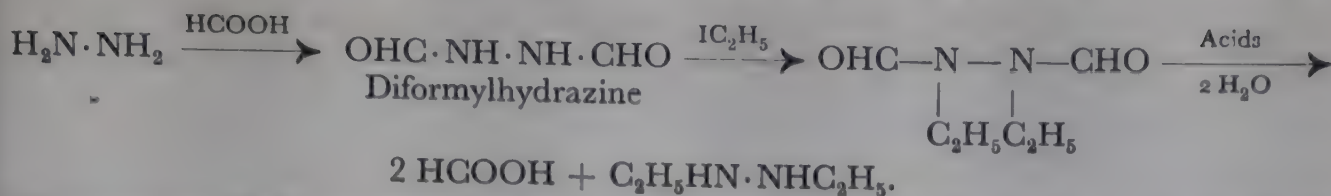


Their behaviour towards oxidizing agents is noteworthy. They are oxidized by mercuric oxide to *tetrazones*, which are interesting on account of the fact that they contain four nitrogen atoms directly linked to each other in a chain:



The primary and unsymmetrical secondary hydrazines of the *benzene series* are of much greater practical importance than their aliphatic analogues. They are often used as reagents for aldehydes and ketones.

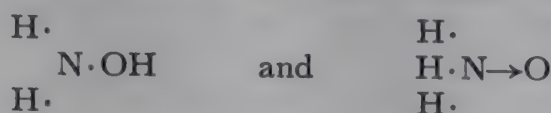
The aromatic symmetrical secondary hydrazine derivatives, the hydrazo-compounds, are likewise of greater importance than the aliphatic ones. The latter can be prepared by the following method:



By the action of alkyl *chlorides* (not bromides or iodides) on hydrazine or dialkylhydrazines it is possible to prepare also trialkyl- and even tetraalkylhydrazines. The lower trialkyl- and tetraalkylhydrazines are colourless liquids of weak to very weak basicity.

III. Alkyl derivatives of hydroxylamine

As is known from inorganic chemistry, the properties of hydroxylamine make it probable that the substance can react in the two tautomeric forms:



Organic compounds are known which are derived from both these forms.

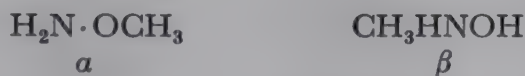
Trialkyl derivatives of the oxide form H_3NO are generally obtained by the action of tertiary amines on hydrogen peroxide:



They usually crystallize well, are easily soluble in water, and reduce silver salts. They reveal, however, their peroxidic nature by their behaviour towards an acidified solution of an iodide which they oxidize, liberating iodine.

The *trialkylamine oxides* combine with acids to form salts, $[(\text{C}_n\text{H}_{2n+1})_3\text{NOH}]\text{X}$, which crystallize well, and dissociate into ions in aqueous solution. Certain of these compounds, of the type $[\text{R}'\text{R}''\text{R}'''\text{N} \cdot \text{OH}]\text{X}$, can be resolved into optically active forms.

N-Alkyl and O-alkyl compounds are derived from the hydroxy-form of hydroxylamine, $\text{H}_2\text{N} \cdot \text{OH}$. Thus, O-METHYL-HYDROXYLAMINE (α -methyl-hydroxylamine) is a strongly alkaline liquid, boiling at 68° , and forming a hydrochloride which melts at 128° :



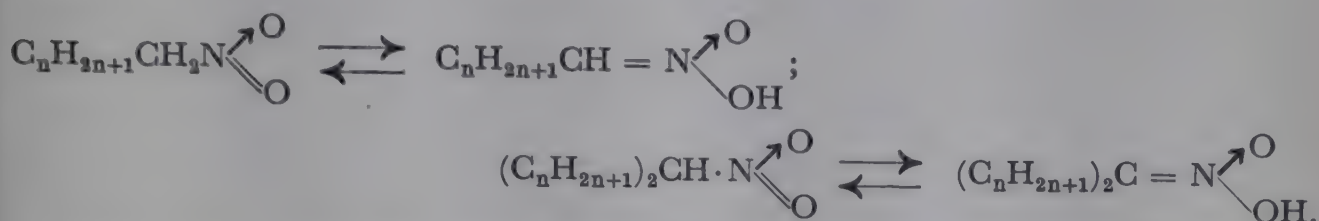
N- or (β)-METHYL-HYDROXYLAMINE is a crystalline substance (m.p. 42°). It is much more difficult to split off the alkyl group from this compound by heating with acids than from its isomeride.

IV. Aliphatic nitro-compounds

The *aliphatic nitro-compounds* are more difficult to obtain than the corresponding aromatic compounds. For this reason they have not the importance in preparative chemistry that is associated to such a great extent with the aromatic nitro-compounds. Yet they command attention in certain directions. The extent to which the presence of certain groups of atoms can influence the reactivity of neighbouring atoms, can be more clearly followed in these compounds than in those which have been previously described.

The direct introduction of nitro-groups ($-\text{NO}_2$) into aliphatic hydrocarbons is often possible by means of dilute or concentrated nitric acid. The nitration is particularly easy with hydrocarbons containing secondary and tertiary carbon

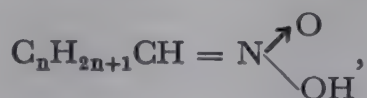
Only the tertiary nitro-compounds, however, are unaffected by treatment with caustic alkalis. The primary and secondary nitro-compounds dissolve, forming salts. If alcoholic caustic soda is used the sodium salt is deposited in the solid form. The exhaustive researches of Michael, Nef, Holleman, and especially Hantzsch have proved that salt-formation with the nitro-compounds is accompanied by an intramolecular rearrangement. The primary and secondary nitro-compounds can react in two desmotropic forms, the one being formed from the other by the wandering of a hydrogen atom, attached to the same carbon atom as the nitro-group, to the oxygen of the nitro-group:



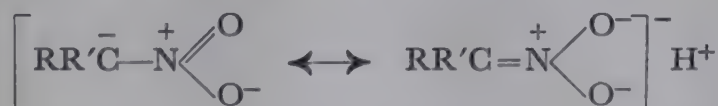
It is easy to see that tertiary nitro-compounds would be incapable of this isomerization.

For purely aliphatic nitro-derivatives it has not yet been possible to isolate the two tautomeric forms in a pure state. This has however been done for mixed aromatic-aliphatic nitro-compounds, such as phenylnitromethane. The two forms show quite different behaviour. The one, stable form is neutral, dissolves very slowly in caustic soda, and its solutions are non-conductors. The second, labile form, is acidic, conducts an electric current well, and dissolves readily in sodium carbonate.

The acidic form of the nitro-compound is called the *aci-form*. There can be no doubt, that of the two isomerides, it has the formula:



since it is generally observed that hydrogen which is linked with oxygen can be substituted by a metal, thus endowing the compound concerned with acidic properties. The compound can also be formulated in mesomeric states corresponding to the following formulæ (hybrid-structure):



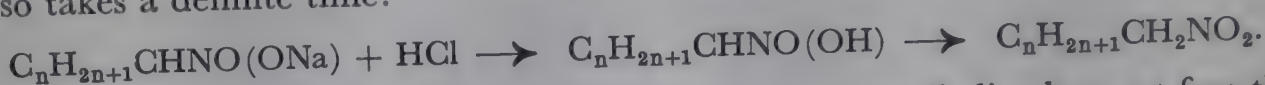
Another name for aci-nitro-compounds is "nitronic" acids, this name expressing

the analogy between the group $=\text{N}\begin{array}{c} \nearrow \text{O} \\ \searrow \text{OH} \end{array}$ and the carboxyl group $-\text{C}\begin{array}{c} \nearrow \text{O} \\ \searrow \text{OH} \end{array}$.

Primary and secondary aliphatic nitro-compounds are therefore to be regarded as substances which occur in neutral and acidic tautomeric forms, which are very easily converted into each other. Such compounds are called *iso-forms*. It is characteristic of iso-forms that, whilst they themselves are neutral and form non-conducting solutions, they give neutral, or nearly neutral alkali salts. This phenomenon can only be explained by supposing that the iso-forms and their salts

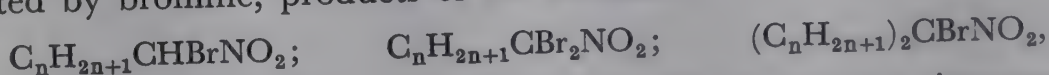
are derived from constitutionally different molecules since the salts of weak acids with strong bases always react strongly alkaline owing to hydrolysis.

It is also a characteristic of the iso-forms that their "neutralization" is not an instantaneous reaction, but requires a definite time for its completion. True acids are neutralized by alkalis *instantaneously*, since, in this case, the reaction takes place between ions. Nitro-compounds, on the other hand, dissolve *slowly* in alkalis. Before the alkali salts can be formed, the molecule must rearrange into the aci-form. This transformation is a time reaction. Only to the extent to which it has taken place is neutralization possible. The reverse process of the re-formation of the ordinary nitro-form from the aci-form of the nitro-compound also takes a definite time:



If the calculated amount of mineral acid is added to the alkali salt to set free the nitronic acid, the latter remains in solution for a considerable time, but slowly isomerizes to the more stable nitro-form.

The phenomena which have been considered above show that the nitro-group must affect the character and reactivity of the hydrogen atoms which are attached to the same carbon atom. It makes the hydrogen atoms labile, capable of wandering. This is also shown in the behaviour of the nitro-compounds towards the halogens. In primary and secondary nitro-compounds the labile hydrogen atoms are easily substituted by bromine, products of the formulæ:



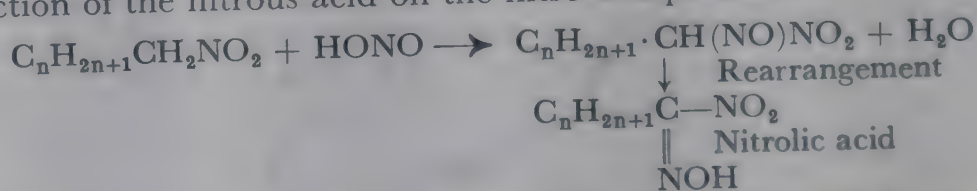
being obtained. The first of these is still soluble in alkalis. Tertiary nitro-compounds do not take up bromine under these conditions, thus clearly showing that the effect of the nitro-group in making the hydrogen atoms more reactive is confined to those hydrogen atoms which are linked to the same carbon atom as the nitro-group itself.

This is by no means an isolated case. In all branches of chemistry it can be shown that certain groups of atoms exert a "loosening" effect on neighbouring atoms, making them more reactive. To these groups belong, in addition to the nitro-group, e.g. the carboxyl, $-\text{COOH}$, the carbonyl, $>\text{CO}$, the cyanide, $-\text{C}\equiv\text{N}$, and the nitroso-group, $-\text{N}=\text{O}$. They are all acid radicals and contain unsaturated linkages. They are commonly called "*negative substituents*".

If a group of atoms is attached to *two* negative radicals of this kind, such as the methylene group in the compound $\text{N}\equiv\text{C}-\text{CH}_2-\text{COOH}$, it is characterized by specially great reactivity. Cases of this kind will be frequently met with.

Reactions of the primary and secondary nitro-compounds with nitrous acid, which can serve to recognize the nature of these substances, also depend upon the activating action of the nitro-group.

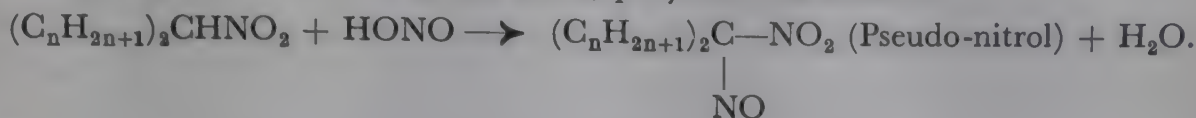
If a suspension of a *primary* alkyl-nitro-compound is mixed with a solution of a *nitrite*, and the mixture is acidified with sulphuric acid, a *nitrolic acid* is produced by the action of the nitrous acid on the nitro-compound:



The nitrolic acids can be extracted with ether, and form red alkali salts. This

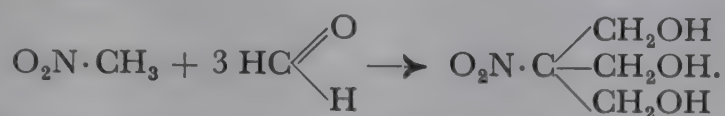
colour reaction is so sensitive that it is suitable for the detection of very small amounts of primary nitro-compounds.

Under the same reaction conditions, *secondary* nitro-compounds are converted into *pseudo-nitrols*, which in solution, and in the liquid state are *blue* or *greenish blue* in colour, but are colourless in the solid, polymerized form:



Tertiary nitro-compounds do not react with nitrous acid.

Finally, primary and secondary nitro-compounds are able to add on to aldehydes by means of the hydrogen atoms rendered mobile by the presence of the nitro-group. Thus nitromethane combines with three molecules of formaldehyde, according to the equation:



(This nitro-tertiary-butylglycerol is readily converted into the trinitrate, a valuable modern explosive.)

The aliphatic nitro-compounds are liquids with a pleasant smell. They can be distilled without decomposition. They are only slightly soluble in water, and their solutions are neutral.

There are, moreover, numerous aliphatic nitro-compounds in which more than one nitro-group is attached to a carbon atom, e.g. $\text{CH}_2(\text{NO}_2)_2$, dinitromethane, $\text{CH}(\text{NO}_2)_3$, trinitromethane, or nitroform, and $\text{C}(\text{NO}_2)_4$, *tetranitromethane*.

TETRANITROMETHANE is obtained, for example, from acetic anhydride and nitrogen pentoxide, or very concentrated nitric acid. There are also many other methods of obtaining it. It is a liquid (m.p. 13° ; b.p. 126°), and is very stable, but if mixed with substances rich in carbon it burns explosively. It has the power of combining with many unsaturated compounds to give coloured addition products, and is therefore used as a reagent for the detection of such substances.

The simplest *unsaturated* nitro-compound is *nitroethylene*, $\text{CH}_2 = \text{CHNO}_2$. It is obtained from β -nitroethyl alcohol by removing water from it by means of phosphorus pentoxide or sodium bisulphate (H. Wieland). It has a powerful irritating action on the mucous membranes and has a strong tendency to polymerize, properties which recall those of the simplest unsaturated aldehyde, acrolein, $\text{CH}_2 = \text{CH}\cdot\text{CHO}$. Its boiling point is 98.5° .

CHAPTER 7

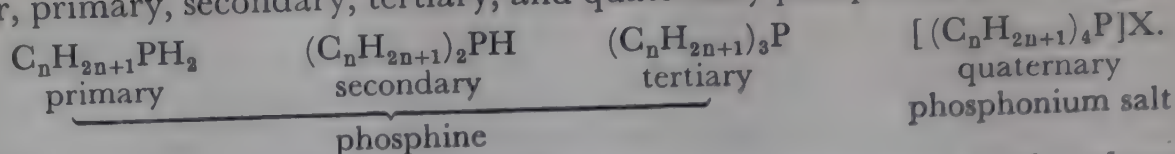
ORGANIC DERIVATIVES OF OTHER ELEMENTS¹

Aliphatic phosphorus compounds

The *alkyl phosphorus compounds*, of which the investigation is due particularly to A. W. Hofmann, Cahours, and A. Michaelis, are derived from the gas phosphine, PH_3 , and are formally comparable with the amines. As in the case of the

¹ A. and D. GODDARD, *Organometallic Compounds. Derivatives of the Elements of Group I to IV*, (1936), London. — KRAUSE, VON GROSSE, *Die Chemie der metallorganischen Verbindungen*, Berlin, (1937).

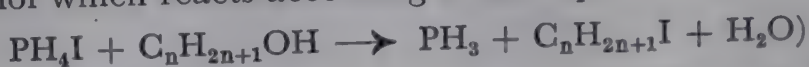
latter, primary, secondary, tertiary, and quaternary phosphines are distinguished:



Tertiary phosphines and quaternary phosphonium salts are produced together by the alkylation of phosphine with alkyl halides. The tertiary phosphines are obtained particularly smoothly, and free from their primary and secondary analogues, by the action of phosphorus trichloride on alkylmagnesium salts [or the zinc dialkyls, $(C_nH_{2n+1})_2Zn$]:



The primary and secondary alkylphosphines are obtained by heating together alkyl halides and phosphine (or a mixture of phosphonium iodide, PH_4I , and alcohol which reacts according to the equation



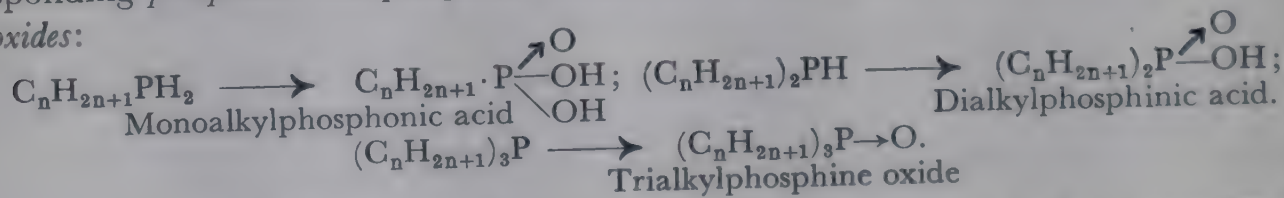
in the presence of a metal oxide, e.g. zinc oxide. The alkylation does not then proceed beyond the formation of the dialkyl phosphine.

The phosphines are liquids, insoluble in water, with a strong, characteristic odour. (Methylphosphine is a gas at ordinary temperatures, b.p. -14°). The phosphines are poisonous. Although they do not react alkaline towards litmus, and are thus sharply differentiated from the aliphatic amines, they form well-crystallized phosphonium salts with acids.

These can be supposed to have a constitution similar to the ammonium salts, and can be written as $[C_nH_{2n+1}PH_3] X$, etc.

Phosphine is a much weaker base than ammonia, as is shown, for example, by the fact that the phosphonium salts are decomposed by water. The salts of the primary phosphines are similarly affected by water, but the more strongly alkylated secondary and tertiary phosphines give stable phosphonium compounds. The quaternary phosphonium bases $[(C_nH_{2n+1})_4P] OH$ are as strong bases as the tetraalkylammonium hydroxides. It is a general rule that the hydroxides of alkylated complex ions are among the strong bases (cf. for example, sulphonium, tetraalkylammonium, tetraalkylarsonium, tetraalkylstibonium bases).

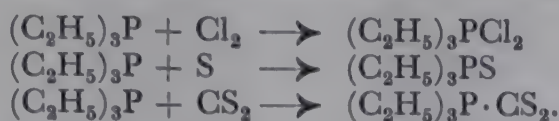
All the phosphines are very unsaturated and readily oxidized, properties which are also shared by phosphine itself. They eagerly take up oxygen from the air, and many are so rapidly oxidized by it that they inflame. By the action of nitric acid, both primary and secondary phosphines are converted into the corresponding *phosphonic* and *phosphinic acids*, and the tertiary phosphines into *phosphine oxides*:



The *monoalkylphosphonic* and *dialkylphosphinic acids* are very stable, crystalline substances, and are strong acids. They are easily soluble in water. The monoalkylphosphonic acids are dibasic, and the dialkylphosphinic acids, monobasic.

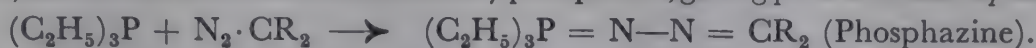
The trialkylphosphine oxides are colourless, crystalline substances, and can be formally compared with the amine oxides, $(C_nH_{2n+1})_3N \rightarrow O$. They differ from the latter, however, in the fact that their oxygen is much more strongly held,

so that they cannot be reduced by the ordinary reducing agents. This is due to the great affinity of phosphorus for oxygen, and its endeavour to remain in the pentavalent state. The tendency of the tertiary phosphines easily to add other substances is to be ascribed to the same cause. With chlorine, trialkylphosphine dichlorides are formed; with sulphur, trialkylphosphine sulphides, and with carbon disulphide, especially characteristic red addition products:

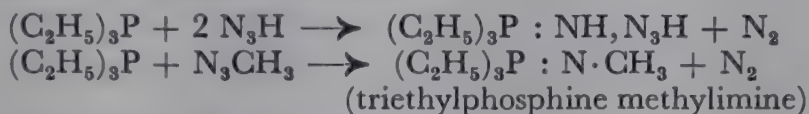


The addition of alkyl halides to the tertiary phosphines also belongs to this group of reactions: $(\text{C}_2\text{H}_5)_3\text{P} + \text{IC}_2\text{H}_5 \longrightarrow [(\text{C}_2\text{H}_5)_4\text{P}]\text{I}$.

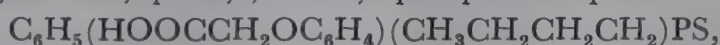
H. Staudinger has shown that the tendency for addition shown by the tertiary phosphines also extends to certain compounds containing nitrogen. Aliphatic diazo-compounds (see p. 293) add on in some cases to the tertiary phosphines, giving products called *phosphazines*:



In a similar way, hydrazoic acid, and its organic derivatives the azides, can add on to tertiary phosphines, the products being *phosphine imines*; when hydrazoic acid is used, the corresponding hydrazoic acid salts are obtained:



Phenyl-(*p*-carboxymethoxy-phenyl)-*n*-butyl-phosphine sulphide:



which, in steric structure corresponds to the amine oxides, has been resolved into optically active forms.

Aliphatic arsenic compounds¹

By the successive substitution of the hydrogen atoms of arsine by alkyl groups, *primary*, *secondary*, and *tertiary arsines* are obtained, and finally the quaternary arsonium salts:

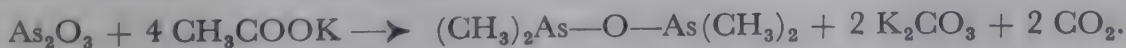


The arsines differ from the amines still more than do the phosphines. The primary, secondary, and tertiary compounds are no longer bases, and do not have the power of forming salts. The quaternary arsonium hydroxides alone are strong bases.

Primary arsines are obtained from monoalkylarsonic acids $\text{C}_n\text{H}_{2n+1}\text{AsO}_3\text{H}_2$, or monoalkylarsine dichloride by reduction (zinc and dilute acid):



A secondary arsine compound is obtained in the form of its oxide by heating potassium acetate with arsenious oxide:



The dimethylarsine derivatives are called, on account of their repulsive smell, *cacodyl compounds*. The above-mentioned oxide was obtained by Cadet (1760)

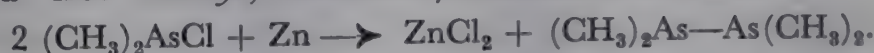
¹ Bibliography on aliphatic and aromatic arsenic compounds: A. BERTHEIM, *Handbuch der organischen Arsenverbindungen*, Stuttgart, (1913). — G. W. RAIZISS and J. L. GAVRON, *Organic Arsenical Compounds*, New York, (1923). — J. NEWTON-FRIEND, *Derivatives of Arsenic*, vol. 11 part 2 of the Text-book of Inorganic Chemistry, London, (1930).

when he distilled potassium acetate and arsenious oxide, but Bunsen, in his famous research, first elucidated the nature of the cacodyl compounds. He showed that a compound radical, C_2H_6As- , was present in cacodyl oxide, which was transferred unchanged to other derivatives. This discovery was of great importance in connection with the radical theory, then under consideration.

Cacodyl chloride (dimethylarsine chloride) is easily obtained from cacodyl oxide and hydrochloric acid:



If this is treated with metals, e.g. zinc or mercury, it gives up its chlorine to the metal, and "free" *cacodyl*, tetramethyldiarsine is formed:



By reduction of cacodyl chloride with platinized zinc and hydrochloric acid, dimethylarsine, or "cacodyl hydride" is formed:



The *tertiary arsines* and the *quaternary arsonium compounds* obtained from them, are much more easily prepared. To obtain the former, the reaction between arsenic trichloride and alkylmagnesium salts, or zinc dialkyls may be employed:

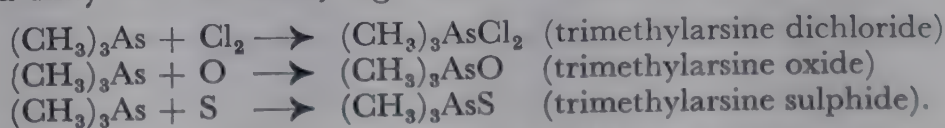


If sodium arsenide is heated with methyl iodide, the chief product is quaternary methylarsonium iodide, whilst trimethylarsine is formed in smaller quantities:



All the arsines are very poisonous, particularly the more volatile ones. In carrying out work with these substances care must be taken not to breathe the vapours.

MONOMETHYLARSINE, CH_3AsH_2 (b.p. 20°), and DIMETHYLARSINE, $(CH_3)_2AsH$ (b.p. 35°), are very easily oxidized and readily take up oxygen from the air. They do not form salts with acids. TRIMETHYLARSINE also is not a base. It easily takes up halogens, oxygen, and sulphur, however, forming derivatives of pentavalent arsenic, and may add on salts, e.g. mercury chloride:



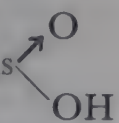
The tertiary arsines combine with alkyl halides to give the *quaternary arsonium compounds*. These are solid, well-crystallized, very stable compounds. Moist silver oxide liberates the free arsonium hydroxides from the halides, which approach the tetraalkylammonium bases as far as degree of dissociation is concerned.

The monoalkylarsonic and dialkylarsinic acids may be regarded as oxidation products of the arsines. They are used in medicine, though their aromatic analogues are far more important in this respect.

METHYLARSONIC ACID, $CH_3AsO_3H_2$, is obtained by methylating sodium arsenite:



It is a well-crystallized, solid, dibasic acid. Its sodium salt occurs in commerce as an arsenical preparation. It is, like most arsenic compounds containing pentavalent arsenic, much less toxic than those containing trivalent arsenic, and is often used in the treatment of skin diseases, anæmia, chlorosis, and tuberculosis, in

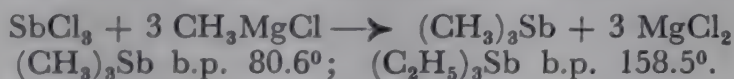
place of inorganic arsenic preparations. The compound is used in the same instances as dimethylarsinic acid, or cacodylic acid, $(\text{CH}_3)_2\text{As}$ 

CACODYLIC ACID is formed by the oxidation of various cacodyl derivatives, e.g. cacodyl oxide. It is a solid, odourless substance, and is weakly acidic. It can, however, also react as a base towards acids, forming salt-like compounds with strong acids (e.g. $(\text{CH}_3)_2\text{AsO}_2\text{H} \cdot \text{HCl}$). In medicine the sodium salt is chiefly used.

Aliphatic antimony and bismuth compounds

The more metallic the nature of an element, the more unstable are, in general, its alkyl derivatives. This is clear, for example, from a comparison of the organic derivatives of the elements of the nitrogen group.

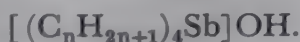
Of the alkyl compounds of antimony¹ the *tertiary stibines* and *quaternary stibonium salts* are fairly easily prepared, and have been more thoroughly investigated. The lower members of the trialkylstibines are repulsive smelling liquids, insoluble in water, and spontaneously inflammable in air, obtained by acting on alkylmagnesium salts with antimony trichloride:



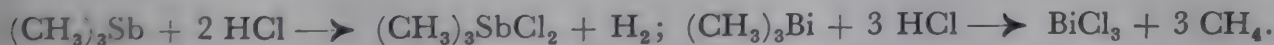
Their strongly unsaturated character is shown by the ease with which they combine with oxygen, sulphur, and the halogens to give derivatives of pentavalent antimony. These reactions are very violent:



Trialkylstibines also add on alkyl halides very easily; the *tetraalkylstibonium salts* thus obtained correspond completely to the analogous phosphonium and arsonium compounds. Thus, by the action of silver oxide they give tetraalkylstibonium hydroxides, which are strong bases, remarkable for their stability:



Whilst the trialkylstibines are not decomposed by mineral acids, but combine with the negative ion of the acid, becoming converted into the more stable derivatives of pentavalent antimony, the *trialkylbismuthines* are decomposed by acids with the formation of hydrocarbons:



Bismuth trialkyls thus behave as true organo-metallic compounds, like the alkylmagnesium salts, or zinc dialkyls, which decompose in a similar way when acted upon by acids.

Organic derivatives of pentavalent bismuth are not known. The trialkylbismuthines have no tendency to add on alkyl halides.

The bismuth trialkyls are obtained by the action of bismuth trichloride on the zinc dialkyls:



$(\text{CH}_3)_3\text{Bi}$ boils at 110° , explodes on heating in air, and has an unpleasant smell. $(\text{C}_2\text{H}_5)_3\text{Bi}$ boils under 79 mm pressure at 107° , fumes in air, and inflames.

Aliphatic silicon compounds (Silanes)

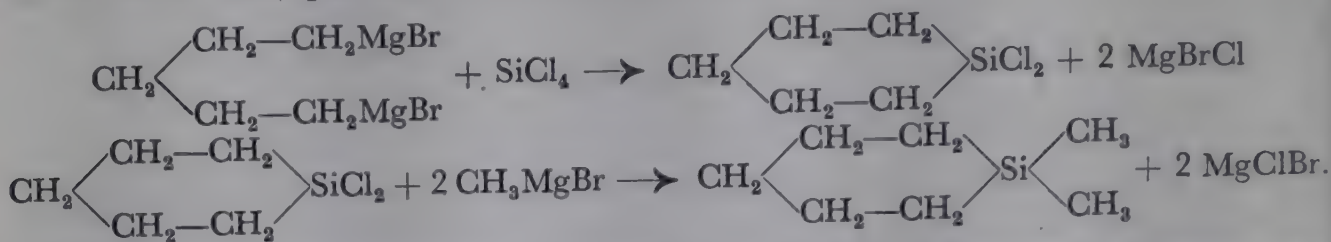
A number of different methods are available for the preparation of organic silicon derivatives, the most suitable one for any given case being chosen. The

¹ F. G. MORGAN, *Organic compounds of arsenic and antimony*, London, (1918). — W. G. CHRISTIANSEN, *Organic Derivatives of Antimony*, New York, (1925).

reaction between silicon tetrachloride and zinc dialkyls has been frequently used to obtain tetraalkylsilanes (Friedel, Crafts, Ladenburg):



In many cases the action of alkylmagnesium salts on silicon tetrachloride is useful (Kipping, Bygdén). This reaction has not only been used for the simpler syntheses, but also for the preparation of cyclic silicon compounds, where the silicon atom takes part in the formation of the ring:



Finally, silicon alkyls are obtained by acting on a mixture of silicon tetrachloride and an alkyl halide with sodium:



The boiling points of those tetraalkylsilanes which are volatile without decomposition, are a little, but not much, higher than those of the corresponding hydrocarbons:

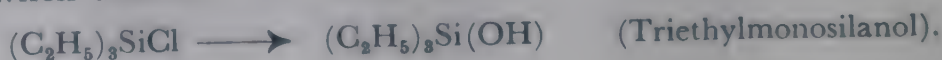
	b.p.		b.p.
$(\text{CH}_3)_4\text{Si}$	26.5°	$(\text{CH}_3)_4\text{C}$	9.0°
$(\text{CH}_3)_3\text{Si}(\text{C}_2\text{H}_5)$	63.0°	$(\text{CH}_3)_3\text{C}(\text{C}_2\text{H}_5)$	49.6°
$(\text{CH}_3)_3\text{Si}(\text{n-C}_3\text{H}_7)$	89.5°		
$(\text{CH}_3)_2\text{Si}(\text{C}_2\text{H}_5)_2$	95.8°	$(\text{CH}_3)_2\text{C}(\text{C}_2\text{H}_5)_2$	86.5°
$(\text{CH}_3)_3\text{Si}(\text{n-C}_4\text{H}_9)$	115.1°		
$(\text{CH}_3)_2\text{Si}(\text{C}_2\text{H}_5)(\text{n-C}_3\text{H}_7)$	121.0°		
$(\text{CH}_3)_3\text{Si}(\text{i-C}_5\text{H}_{11})$	131.5°		
$(\text{CH}_3)_2\text{Si}(\text{C}_2\text{H}_5)(\text{i-C}_4\text{H}_9)$	138.0°		
$(\text{C}_2\text{H}_5)_4\text{Si}$	153.0°		
$(\text{CH}_3)_3\text{Si}-\text{Si}(\text{CH}_3)_3$	113.0°	$(\text{CH}_3)_3\text{C} \cdot \text{C}(\text{CH}_3)_3$	106.0°
$(\text{CH}_3)_3\text{Si}(\text{C}_6\text{H}_5)$	171.6°	$(\text{CH}_3)_3\text{C}(\text{C}_6\text{H}_5)$	168.2°
$(\text{CH}_3)_2\text{Si}(\text{C}_2\text{H}_5)(\text{C}_6\text{H}_5)$	198.0°	$(\text{CH}_3)_2\text{C}(\text{C}_2\text{H}_5)(\text{C}_6\text{H}_5)$	189.0°
$(\text{C}_2\text{H}_5)_3\text{Si}(\text{C}_6\text{H}_5)$	238.3°	$(\text{C}_2\text{H}_5)_3\text{C}(\text{C}_6\text{H}_5)$	221.0°

The *tetraalkylsilicon compounds* are very stable. In their properties and chemical reactions they show analogies with the aliphatic hydrocarbons. These analogies, however, fall into the background in certain simple derivatives of the alkylsilanes. Our knowledge of these compounds has been extended within recent years especially by the work of A. Stock.

By the action of chlorine on tetraethylsilane ("silicononane"), Friedel and Crafts obtained a "*silicononyl chloride*", $(\text{C}_2\text{H}_5)_3\text{Si} \cdot \text{C}_2\text{H}_4\text{Cl}$, or a mixture of isomerides, which, like the alkyl halides, has the chlorine linked to a carbon atom. This chlorine atom is replaced by an acetyl group by treatment with potassium acetate, and by hydrolysis of the acetate ester thus obtained, a silicon-containing alcohol, "*silicononyl alcohol*" (b. 122 at 751 mm) is produced:



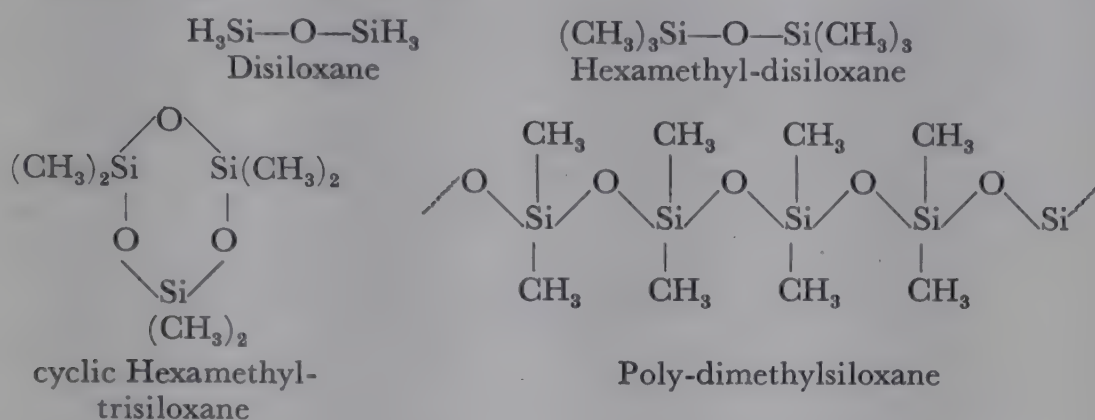
Hydroxyl derivatives of the alkylsilanes are also known in which the $-\text{OH}$ group is linked to silicon. *Triethylmonosilanol* was obtained from triethylsilicon chloride. It is a liquid smelling like camphor, which, like the alcohols, gives hydrogen when treated with sodium:



Recently, the so-called "*Siloxanes*" and "*Silicones*" have been exhaustively investigated and made available for practical purposes, especially through the work of American firms (Dow Corning Co. and General Electric Co.).

It is not possible to prepare high-molecular organic silicon compounds with many silicon atoms linked to each other, because the Si—Si-bond becomes increasingly more unstable as the number of Si-atoms is increased. Compounds containing more than six Si-atoms in a chain can hardly, if ever, be prepared; moreover, alkalis hydrolyse the Si—Si bonds with formation of hydrogen and the corresponding oxides.

However, a practicable way to obtain high-polymeric Si-rich organic compounds was found in the preparation of the so-called "*Polysiloxanes*". A siloxane is a silicon compound in which the silicon atoms are connected by oxygen-bridges and the remaining valencies of the silicon atoms are saturated with hydrogen or organic radicals (alkyl or aryl groups):

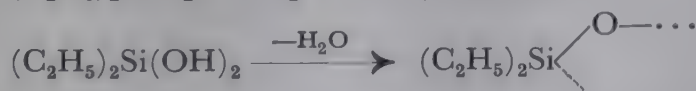


Compounds such as poly-dimethylsiloxane, in which the chains consist of $-\text{R}_2\text{SiO}-$ groups have received the name *Silicones*.

The silicones are prepared by the action of alkyl-Mg salts on SiCl_4 in a way so that the relative quantities of the starting materials used lead preferentially to the formation of dialkylsilicon dichlorides:

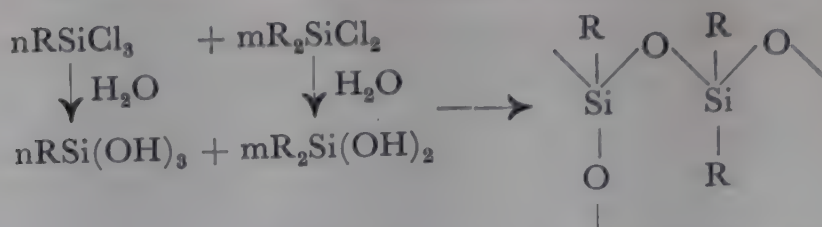


The dialkylsilicon dichlorides can be hydrolysed to the corresponding hydroxy-compounds, the silicols, which are unstable and polymerize immediately to poly-dialkylsiloxanes, i.e. silicones:



The rapidity with which the silicol groups unite to form chains depends on the nature of the organic radicals. Alkylsilanediols with small alkyl radicals polymerize so quickly that up to now it has not been possible to isolate the monomeric compounds. In contrast, diphenylsilanediol is a relatively stable, crystalline substance, which only begins to give off water quickly at 100° .

The polymerization of organic silanediols can proceed differently according to the conditions and leads either to chain- or ring-built polymers. If mixtures of monoalkyl- and dialkylsilicon chlorides are hydrolysed, silicone molecules in the form of nets can be obtained:



The silicones have acquired great practical importance. Depending on the starting materials and conditions of polymerization, products can be obtained with very different properties. There are methylsilicone polymers which have an oily or greasy consistency and which are suitable as heat-stable lubricants, insulating and packing materials. Others show a rubber- or caoutchouc-like nature, possessing great elasticity, which is only little changed over the temperature range -57 to $+260^\circ\text{C}$. Furthermore, synthetic resins on a basis of silicone are produced (silicone resins), which are suitable for heat-stable pigments and lacquer preparations or for the production of resistances and insulators in the electrical industry. Surfaces of articles in everyday use (wood, cotton, glass, ceramic ware, etc.) which are impregnated with a film of silicone, have hydrophobic properties and are impervious to water.

Thus, there arises in the silicones a new group of substances which combines in a fortunate way the properties of both organic and inorganic compounds.

Aliphatic Germanium compounds

For a long time *tetraethylgermanium*, which was prepared by C. Winkler from germanium tetrachloride and diethylzinc, was the only known organic germanium compound:

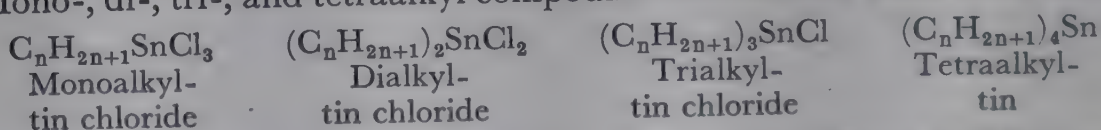


It is a liquid which smells of leeks, and boils at 160° . It is stable in the air.

Many similar germanium alkyls have been synthesized more recently from germanium chloride and alkylmagnesium salts, e.g. tetramethylgermanium (b. 43.4°), tetrapropylgermanium (b.p. 74.6 , 225°), and tetra*iso*amylgermanium, (b.p. 19 , 163 – 164°), etc. CH_3GeCl_3 , $(\text{CH}_3)_2\text{GeCl}_2$, and $(\text{CH}_3)_3\text{GeCl}$ are also known.

Organic compounds of tin

Mono-, di-, tri-, and tetraalkyl compounds are derived from tetravalent tin.



Tin tetraalkyls are the easiest to prepare, as the action of zinc dialkyls, or alkylmagnesium salts on stannic chloride gives mainly these, the completely alkylated, compounds:

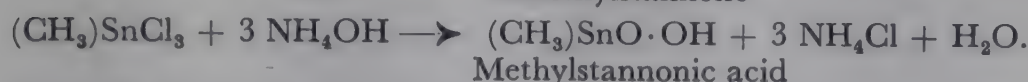
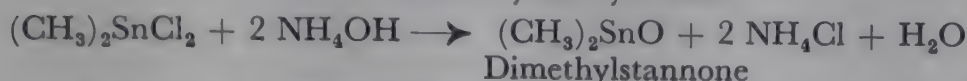
$$\text{SnCl}_4 + 4 \text{CH}_3\text{MgCl} \longrightarrow \text{Sn(CH}_3)_4 + 4 \text{MgCl}_2.$$

If the stannic chloride is present in excess, the product consists partly of trialkyltin salts (P. Pfeiffer).

Mixtures of dialkyltin iodides, trialkyltin iodides, and tetraalkyltins are obtained when alkyl iodides act on finely-divided tin, or tin-sodium alloys. According to the conditions of the experiment one or other of these products is obtained in excess.

The first members of the series of tin tetraalkyls are colourless, ethereal smelling liquids, insoluble in water, and stable in air: $(\text{CH}_3)_4\text{Sn}$ boils at 78° , $(\text{C}_2\text{H}_5)_4\text{Sn}$ at 181° .

In the alkyltin salts, the halogen atoms are very loosely held, as in stannic chloride and can easily be replaced. Alkalis (caustic potash, ammonia) convert them into hydroxides; the trialkyltin salts give *trialkyltin hydroxides*, the dialkyltin salts give *dialkylstannones*, and the monoalkyltin salts give *alkylstannonic acids*:



The trialkyltin hydroxides are crystalline compounds which can be distilled. They dissolve in water giving an alkaline solution, and are neutralized by acids giving trialkyltin salts:



The dialkylstannones also react with acids to give dialkyltin salts. They are amorphous solids. The likewise amorphous and infusible monoalkylstannonic acids dissolve in alkalis.

If the halogen atom is removed from trialkyltin salts by a metal, *hexaalkyldistannanes* are produced, which very probably possess two tin atoms directly linked to each other (Ladenburg, Grüttner):



They are formally comparable with hexamethyl-silicoethane, $(\text{CH}_3)_3\text{Si}—\text{Si}(\text{CH}_3)_3$ and cacodyl, $(\text{CH}_3)_2\text{As}—\text{As}(\text{CH}_3)_2$, and share with these the property of reacting easily with halogens, or halogen hydracids, trialkyltin halides being re-formed.

The first organic compound of *divalent* tin to be discovered was tin diethyl, which can be obtained, for example, by the action of stannous chloride on ethylmagnesium bromide:



The substance is a yellow oil. Divalent tin compounds with aromatic radicals, such as diphenyltin, $\text{Sn}(\text{C}_6\text{H}_5)_2$, and di-*p*-tolyltin, appear to be better characterized. They are brilliant yellow amorphous powders, monomolecular, and readily acted upon by oxidizing agents, even by air.

Pope and Peachey, in some interesting work, have shown that trialkyltin salts with three different alkyl groups can be resolved into *optically active forms*. The resolution of *methyl-ethyl-propyl-tin iodide*, $(\text{CH}_3)(\text{C}_2\text{H}_5)(\text{C}_3\text{H}_7)\text{SnI}$ was carried out with *d*-camphorsulphonic acid. The silver salt of the latter reacts with the methyl-ethyl-propyl-tin iodide to give the *d*-camphorsulphonate of the trialkyltin base, which easily crystallizes out. After addition of potassium iodide to this salt the optically active methyl-ethyl-propyl-tin iodide is precipitated. The highest rotation observed is $[\alpha]_{\text{D}} = +23^\circ$.

The space structure of such optically active molecules may be supposed to be as follows: the tin atom of the methyl-ethyl-propyl-tin salt is inside a tetrahedron, and the four substituents lie at the apices of the tetrahedron. The relationships would thus be analogous to those obtaining for carbon compounds. It is also possible, however, that the three alkyl radicals and the tin atom lie at the apices of an irregular tetrahedron, and the iodine atom lies outside this in a "second sphere". Such a spatial arrangement would also give rise to enantiomorphic forms.

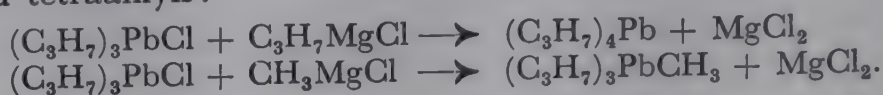
Organic compounds of lead

The alkyl derivatives of lead show considerable similarity with those of tin, both as regards methods of preparation and properties. The most stable are the organic derivatives of *tetravalent lead*. It is only in recent times that derivatives of tri- and divalent lead have been prepared.

The lower *lead tetraalkyls* are best obtained from lead chloride and dialkyl-zinc or alkylmagnesium salts:



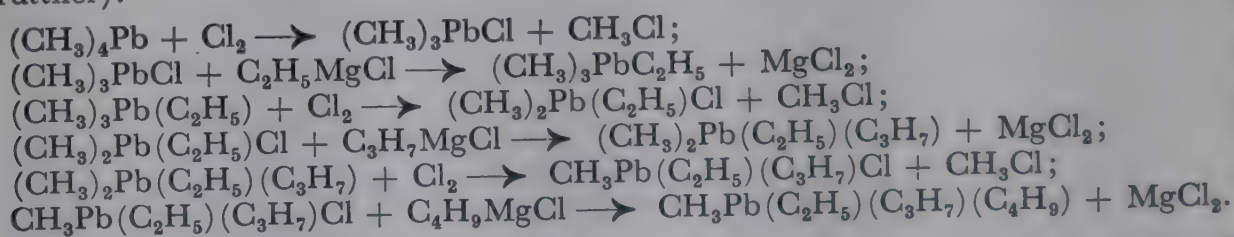
However, when alkylmagnesium salts containing alkyl radicals with three or more carbon atoms are used the method fails, since in this case unsaturated lead alkyls (lead trialkyls, etc.) are preferentially formed. It is, however, easy to add halogens to these unsaturated compounds, and the trialkyllead halides obtained are now capable of reacting with Grignard reagents to give symmetrical or mixed lead tetraalkyls:



Lead tetraalkyls are stable, colourless liquids, with a strong smell. They are not decomposed by water, and are very poisonous.

Tetraethyllead has, since the discovery of its antiknock properties in internal combustion engines (Thomas Midgeley), become of great importance as an addition to motor fuels, especially aviation petrol. For this purpose it is manufactured by the reaction of lead amalgam with ethyl chloride.

The action of halogens on lead tetraalkyls leads to the removal of an alkyl radical, which is replaced by halogen. It is always the smallest alkyl group which is eliminated in this way from mixed lead tetraalkyls. As it is possible, as explained above, to reconvert the trialkyllead salts by means of alkylmagnesium salts into lead tetraalkyls, a combination of these two processes may be used to obtain lead tetraalkyls with four different alkyl radicals (Grüttner):

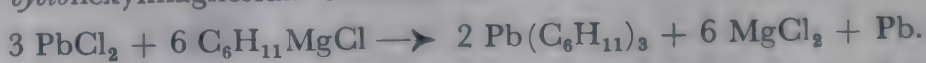


Trialkyllead hydroxides, $(\text{C}_n\text{H}_{2n+1})_3\text{PbOH}$, dissolve in water with a strong alkaline reaction.

By thermal decomposition of tetramethyllead (and trimethylbismuth) Paneth has been able to prepare *free methyl*, $\text{CH}_3\text{—}$, the life-period of which is extraordinarily short (8.4×10^{-3} seconds). The gaseous substance attacks metals (zinc, lead) as well as non-metals (antimony), converting them into alkyl derivatives, such as dimethylzinc, trimethyl-antimony, etc.

From tetraethyllead, *free ethyl* is obtained in a similar way. Its properties are similar to those of methyl.

Organic derivatives of *trivalent lead* are at present only known in small numbers, and combined with more complex organic groups. *Tricyclohexyllead* has been obtained from lead chloride and *cyclohexylmagnesium chloride*:



It crystallizes well, and is lemon-yellow in colour. This compound is coloured on account of its unsaturated character (Krause).

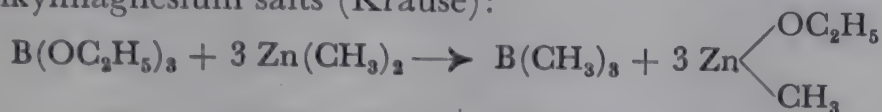
Some organic derivatives of *divalent lead* have been obtained from lead chloride and phenyl- or tolylmagnesium salts in the absence of air.



Diphenyllead and *ditolyllead* are red, amorphous, and monomolecular. They soon become colourless on exposure to air, owing to oxidation. They reduce silver nitrate solution. These reactions give evidence of their strongly unsaturated character.

Organic compounds of boron

Boron trialkyls, $\text{B}(\text{C}_n\text{H}_{2n+1})_3$, can be obtained from esters of boric acid, or boron trichloride by the action of zinc dialkyls, but better by the action of boron trifluoride on alkylmagnesium salts (Krause):



They are colourless liquids, with a characteristic smell, which is reminiscent of radishes and onions. They are oxidized on exposure to air. Their synthesis must therefore be carried out in an atmosphere of nitrogen. When rapidly oxidized they inflame, and burn with a green flame.

Water reacts with the boron trialkyls very slowly. Controlled oxidation by means of atmospheric oxygen gives alkylboron oxides, $\text{C}_n\text{H}_{2n+1}\text{BO}$, which, on boiling with water form the beautifully crystallized alkylboric acids, $\text{C}_n\text{H}_{2n+1}\text{B}(\text{OH})_2$; the latter are also produced when alkylmagnesium salts act upon trialkyl esters of boric acid.

$(\text{CH}_3)_3\text{B}$	gaseous		
$(\text{C}_2\text{H}_5)_3\text{B}$	b.p. 95°	$\text{C}_2\text{H}_5\text{B}(\text{OH})_2$	sublimes at 40°
$(n\text{-C}_3\text{H}_7)_3\text{B}$	b.p. 760 156°	$n\text{-C}_3\text{H}_7\text{B}(\text{OH})_2$	m.p. 107°
$(i\text{-C}_4\text{H}_9)_3\text{B}$	b.p. 760 188°	$i\text{-C}_4\text{H}_9\text{B}(\text{OH})_2$	m.p. 112°

Concentrated hydrochloric acid decomposes the boron trialkyls with formation of hydrocarbons.

The analogue of these compounds in the aromatic series, triphenylboron, possesses the interesting property of adding on alkali metals, giving yellow, crystalline products of the composition $(\text{C}_6\text{H}_5)_3\text{B} \cdot \text{M}^{\text{I}}$ ($\text{M}^{\text{I}} = \text{Li}, \text{Na}, \text{K}, \text{Rb}, \text{Cs}$).

For optically active boron compounds, see Ch. 41.

Organic compounds of aluminium

The best method of preparing the *aluminium trialkyls* is by the action of alkyl halides on aluminium-magnesium alloys. Another method is to act upon alkylmagnesium salts dissolved in ether with anhydrous aluminium chloride:



Triarylaluminium compounds are also formed from mercury diaryls and aluminium.

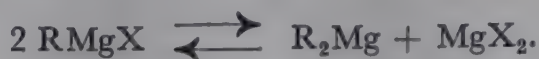
The trimethyl and triethyl compounds are liquids, spontaneously inflammable in air, and decomposing water explosively. $(\text{CH}_3)_3\text{Al}$ boils at 130°, and $(\text{C}_2\text{H}_5)_3\text{Al}$ at 194°.

Organic compounds of magnesium¹

Magnesium dialkyls, $\text{Mg}(\text{C}_n\text{H}_{2n+1})_2$, are not very important in practice. Most

¹ See J. SCHMIDT, *Die organischen Magnesiumverbindungen und ihre Anwendung zu Synthesen*, Stuttgart, vol. 1 (1904), and vol. 2, (1908). — C. COURTOT, *Le magnésium en chimie organique*, Paris, (1927). — FRANZ RUNGE, *Organometallverbindungen*, Part I, *Wissenschaftl. Verlagsges.*, Stuttgart, (1932). — JULIUS SCHMIDT, *Organometallverbindungen*, Part II, *Wissenschaftl. Verlagsges.*, Stuttgart, (1934).

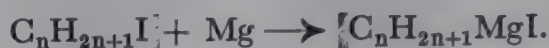
of them are volatile in ether vapour, and can be sublimed *in vacuo*. They are conveniently prepared by the action of magnesium on mercury dialkyls, HgR_2 , (Gilman) or, in some cases, from solutions of alkylmagnesium salts (see below) by precipitation with dioxane (Schlenk). The latter method occasionally gives the required result, since some alkylmagnesium salts undergo partial disproportionation:



Dioxane precipitates alkylmagnesium salts as well as magnesium halides, whilst the magnesium dialkyls remain in solution.

The *alkylmagnesium salts*, $\text{C}_n\text{H}_{2n+1}\text{MgCl}$, discovered by Grignard, are exceedingly important in preparative organic chemistry.

They are usually obtained very easily by adding some ether to a mixture of finely divided magnesium (magnesium wire, turnings, or powder) and an alkyl halide. If the quantity of ether is sufficient the alkylmagnesium salt formed in a short time goes completely into solution:

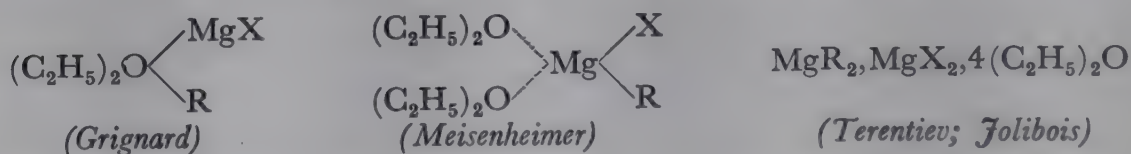


Not all halogen compounds are equally well suited for this reaction. Whilst there are some which react so violently that it is necessary to cool the reacting mixture, there are others which do not combine with magnesium at all. Where the reaction is slow it can be accelerated by the addition of a particle of iodine, or by treating the magnesium with a little of an ether solution of methylmagnesium iodide in order to activate it. Alkyl bromides and iodides react, in general, more readily than the chlorides.

The ethyl ether favours the production of alkylmagnesium salts. It combines with them to give addition products which can be isolated:



The following formulæ have been suggested for these ether compounds:



It is, however, also possible to obtain the alkylmagnesium salts free from ether. To do this, the alkyl halides are made to react with finely divided magnesium in an indifferent solvent, such as xylene, or ligroin, or even without a solvent, by warming. Even then it is convenient to add small amounts of ether or a tertiary amine (e.g. dimethylaniline) which catalytically accelerate the reaction.

Occasionally it is advantageous to use a higher-boiling liquid, such as amyl ether, anisole, or xylene, in place of the lower-boiling ethyl ether in the preparation of alkylmagnesium salts. This makes it possible to carry out the reaction at a higher temperature, which can be a definite aid to the successful carrying out of the process.

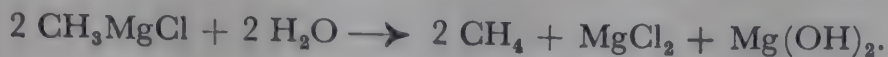
In the solution of a Grignard reagent there is occasionally an equilibrium between the alkylmagnesium salt and magnesium dialkyl, as shown by the equation:



The alkylmagnesium salts are rapidly affected by moisture, being converted by water into a basic magnesium salt and a hydrocarbon:



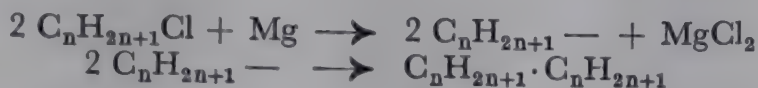
or into a magnesium salt, magnesium hydroxide, and a hydrocarbon:



It is therefore necessary to take great care to exclude moisture during the preparation. Both the magnesium and the alkyl halide, as well as the ether, must be thoroughly dry. Traces of water may also act detrimentally in another way. They favour catalytically a side-reaction, which is often observed in the preparation of solutions of Grignard reagents, and in which a hydrocarbon of higher molecular weight is formed:



Others explain this reaction as follows:



The fact that the alkylmagnesium salts are relatively stable in air makes it possible to prepare and use them without excluding air. This property gives them a great advantage over other metal alkyls, such as the zinc dialkyls, which are spontaneously inflammable in air, and they have now almost entirely replaced the zinc dialkyls, which were formerly used to a considerable extent in organic syntheses.

They are not, however, perfectly stable towards oxygen. They are slowly oxidized by it, especially if the protective ether vapour layer is removed by cooling the reagent in ice. The oxidation takes place with the simultaneous formation of alkyl halide, e.g. in the case of an alkylmagnesium iodide according to the equation:



Water decomposes the oxidation product giving an alcohol and a basic magnesium salt:



If kept in the absence of air, alkylmagnesium salts may be preserved unchanged for years.

Grignard reagents have often been met with in the previous work. They are very valuable reagents for many types of syntheses. Many examples will be quoted later which indicate their many-sided reactivity.

Here only a few reactions will be mentioned.

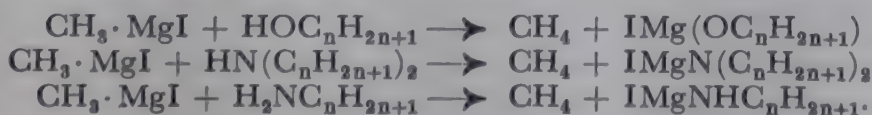
Carbon dioxide is readily taken up by alkylmagnesium salts. If the product is decomposed with water, carboxylic acids are obtained in good yield:



Grignard reagents react with sulphur (in absence of air) to give mercaptans:



In addition to water, other hydroxy-compounds (alcohols, enolic compounds), and primary and secondary amines can react with alkylmagnesium salts:



It is seen from the above equations that in all these reactions 1 mol. of methane is liberated from 1 mol. of alcohol or amine. Since the methane can easily be determined volumetrically the method can be used for the quantitative estimation of active hydrogen atoms (in the —OH or >NH groups). This method is due to Zerewitinoff and Tschugaeff. It should be noted in this connection that primary amines only give 1 mol. of methane in the cold; when heated 2 mols. are usually obtained:

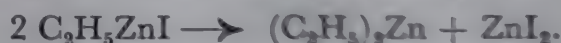


Organic compounds of zinc¹

Alkyl halides usually react fairly easily with freshly prepared zinc filings, especially if some copper powder is added. A small amount of ethyl acetate catalytically accelerates the reaction. The primary products of the reaction are the *alkylzinc salts*:



On distillation these decompose into *zinc dialkyls* and *zinc iodide*:



The *zinc dialkyls*, or "*zinc alkyls*", are clear liquids, which inflame spontaneously in air, and react violently with water. In a similar manner to the alkylmagnesium salts they can be used for the introduction of alkyl groups into other compounds, but they have been replaced more and more by the more easily used alkylmagnesium salts:

$(\text{CH}_3)_2\text{Zn}$	b.p. 46°	$(i\text{-C}_4\text{H}_9)_2\text{Zn}$	b.p. $165\text{--}167^\circ$
$(\text{C}_2\text{H}_5)_2\text{Zn}$	b.p. 118°	$(i\text{-C}_5\text{H}_{11})_2\text{Zn}$	b.p. 220° .
$(n\text{-C}_3\text{H}_7)_2\text{Zn}$	b.p. ca. $148\text{--}150^\circ$		

The alkyl zinc salts, $\text{C}_n\text{H}_{2n+1}\text{ZnX}$, have retained their position in preparative chemistry rather better. They react less violently than the Grignard reagents, and are therefore used even to-day, especially for those reactions where it is desired to isolate intermediate products. They are very suitable for the preparation of ketones from acid chlorides, whilst the alkylmagnesium salts often react with the ketones produced giving tertiary alcohols:



Organic compounds of cadmium

Cadmium dialkyls are obtained by the action of alkylmagnesium bromides on anhydrous cadmium bromide:



They are readily volatile liquids, with a musty smell, and give precipitates when exposed to air or moisture. If they are poured out in air, they fume and occasionally inflame.

$(\text{CH}_3)_2\text{Cd}$	b.p. ₇₅₈ 105.5°	$(\text{C}_2\text{H}_5)_2\text{Cd}$	b.p. _{10.8} 64°
$(n\text{-C}_3\text{H}_7)_2\text{Cd}$	b.p. _{11.8} 84° .		

¹ H. WREN, *Organometallic Compounds of Zinc and Magnesium*, London, (1913).

Organic compounds of mercury¹

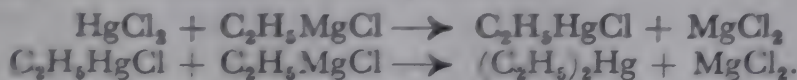
Mercury reacts with alkyl iodides giving *alkylmercury iodides*:



These compounds were formerly converted by the use of zinc dialkyls, into *mercury dialkyls*, but the alkylmagnesium salts are now chiefly used for this purpose:

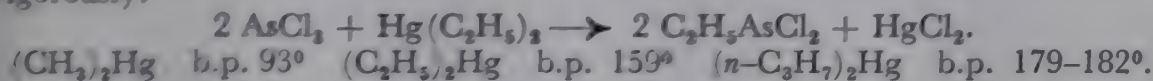


Mercuric halides also react with Grignard reagents, and the mercury dialkyls can therefore in this way be synthesized in one operation:



If in the *second* stage of the reaction another alkylmagnesium salt is used than that employed at first, it is possible under certain conditions to produce mixed mercury dialkyls.

These compounds are liquids, which are stable towards air and water; they are readily volatile, and *exceedingly poisonous*. They were formerly used to bring about a number of syntheses, since they react like the zinc alkyls and the alkylmagnesium salts, but much less vigorously:

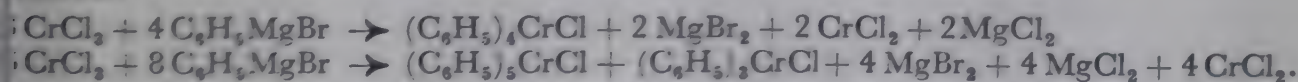


Organic compounds of copper, silver, gold, and platinum

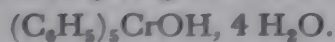
Less is known of organic compounds of copper. *Phenylcopper*, $\text{C}_6\text{H}_5\text{Cu}$, is best prepared from $\text{C}_6\text{H}_5\text{MgI}$ and Cu_2I_2 ; with water it gives biphenyl, with acetyl chloride acetophenone, and with allyl bromide allylbenzene. It thus shows some reactions analogous to those of Grignard reagents. *Phenylsilver*, $\text{C}_6\text{H}_5\text{Ag}$, behaves similarly, and can be obtained from $\text{C}_6\text{H}_5\text{MgBr}$ and AgBr . Methylsilver, CH_3Ag , is formed as a precipitate from silver nitrate and tetramethyllead at low temperatures. At -50° it commences to decompose and detonates weakly at -20° , when ethane is formed. Gold chloride reacts with alkylmagnesium salts with partial formation of dialkylgold chlorides $(\text{C}_n\text{H}_{2n+1})_2\text{AuCl}$. Gold bromide is converted into trimethylgold, $(\text{CH}_3)_3\text{Au}$, by methyl lithium. The chemistry of organic compounds of gold has been extended in more recent times by C. S. Gibson. Compounds of platinum, $(\text{C}_n\text{H}_{2n+1})_3\text{PtI}$, have been described.

Organic compounds of chromium

As Fr. Hein has shown, chromic and chromous chlorides react readily with the Grignard reagents. Thus, by the action of phenylmagnesium bromide on chromic chloride, various well-crystallized polyphenylchromium halides are formed, and the chromic chloride is reduced to the chromous state: The following equations are assumed to represent the reaction:



The polyphenylchromium hydroxides are strong bases. Pentaphenylchromium hydroxide takes up four molecules of water giving the well-crystallized hydrate



The penta-, tetra-, and triphenyl bases all give well-crystallized salts.

Organic compounds of the alkali metals

The interesting *alkali alkyls* were first studied by Schlenk. They are prepared from mercury dialkyls by replacing the mercury by alkali metal. The extra-

¹ See F. C. WHITMORE, *Organic compounds of mercury*, New York, (1921).

ordinary reactivity of the alkali alkyls makes it necessary to use special apparatus to prepare them, in which air and moisture are rigidly excluded. Petrol, for example, may be used as a solvent:



Some sodium alkyls are also formed directly from alkyl chlorides and sodium in petroleum ether at low temperatures, e.g. -10° ; thus, *n*-butyl-, *n*-octyl-, *n*-dodecylsodium, and others were produced in this way.

The sodium alkyls are amorphous powders, insoluble in inert solvents, and which decompose on heating without melting. When exposed to air they inflame immediately, and may burn explosively. Their inflammability decreases with increasing size of the alkyl radical. Numerous representatives of this group, such as NaCH_3 , NaC_2H_5 , NaC_3H_7 , and $\text{NaC}_8\text{H}_{17}$ have been prepared.

The lithium alkyls are also colourless, and some of them can be crystallized. They are, with the exception of methylolithium, soluble in benzene and petrol. They also inflame spontaneously in air. Ziegler has devised a simple method of preparation which consists of the action of metallic lithium on organic halides in an indifferent solvent. The reaction temperature must be kept sufficiently low to prevent the lithium alkyl formed from reacting with unchanged alkyl halide.

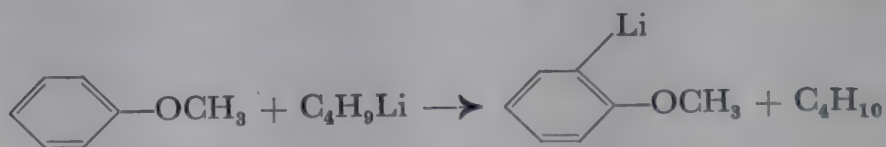


As solvents, often ether or sometimes also benzene or cyclohexane are suitable. Of the alkyl halides, the chlorides are generally the most appropriate, since they are less readily converted than the bromides or iodides into hydrocarbons by a Wurtz-Fittig reaction with the alkyl- or aryllithiums ($\text{RLi} + \text{IR}' \longrightarrow \text{RR}' + \text{LiI}$).

In many cases, as H. Gilman has shown, it is also possible to prepare organic lithium compounds by the action of butyllithium (which is readily obtained in good yield) on aromatic hydrocarbons, phenol ethers, aromatic amines, furan, and thiophen derivatives etc., hydrogen being substituted by lithium:



Thus from $\text{C}_4\text{H}_9\text{Li}$ and naphthalene α - and β -naphthalene-lithium, from anisole *o*-anisole-lithium, from furan 2-furan-lithium etc. are obtained:



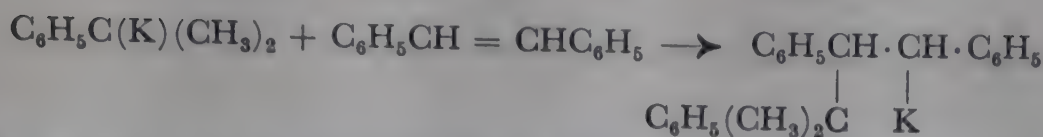
(As a rule Li substitutes hydrogen atoms in ortho positions).

This "transfer reaction" with butyllithium may also be extended to aliphatic halogeno-alkyls, which often react with it to form new lithium alkyls:

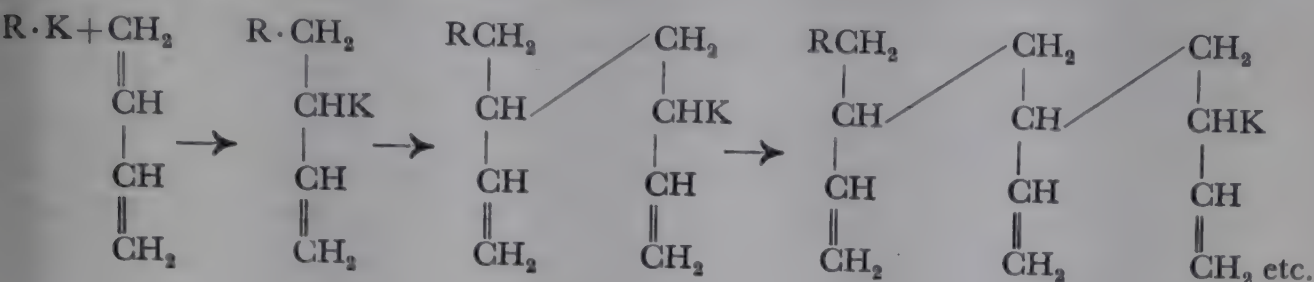


The lithium alkyls have become of considerable importance in recent times, as, owing to their ease of preparation and great reactivity, they are excellently suited for bringing about syntheses (see e.g. p. 173-4 and Ch. 23 (benzene)).

Certain higher alkali alkyls, such as phenyl-*isopropyl*-potassium, $\text{C}_6\text{H}_5\text{C}(\text{K})(\text{CH}_3)_2$, can add on to conjugated double bonds and to those lying adjacent to phenyl radicals (K , Ziegler). An example is the reaction with stilbene:



This reaction may perhaps also explain why alkali metals often cause hydrocarbons to polymerize (cf. for example, the polymerization of isoprene by sodium to synthetic rubber). Such a process may be due to a series of condensations, of which the formulæ below give a schematic representation:



Section II. Compounds with a divalent function

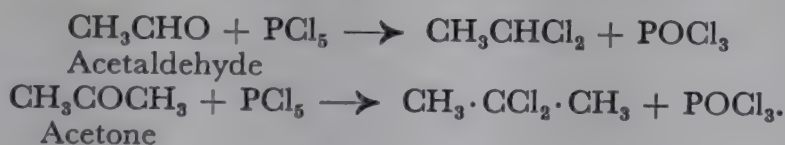
CHAPTER 8

THE DIVALENT HALOGEN FUNCTION:

GEM.-DIHALOGEN DERIVATIVES¹

The *gem.-dihalogen derivatives*, $(\text{C}_n\text{H}_{2n+1})_2\text{CCl}_2$, etc. are usually more difficult to prepare than alkyl halides. They also react as a rule less smoothly, so that they are not nearly so important as the monoalkyl halides.

A general method of preparation for these dihalogen derivatives is the reaction of aldehydes or ketones with phosphorus halides (phosphorus pentachloride, or phosphorus chlorobromide, PCl_3Br_2) or carbonyl chloride:



The addition of halogen hydrides to acetylene hydrocarbons also gives the same products:



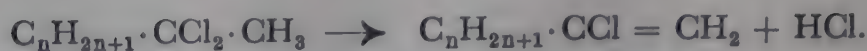
For the preparation of dihalogen derivatives of methane the partial reduction of trihalogen compounds, such as chloroform, bromoform, and iodoform is often used:



Dichloromethane, a modern solvent and extracting agent, is now produced technically by the chlorination of methane.

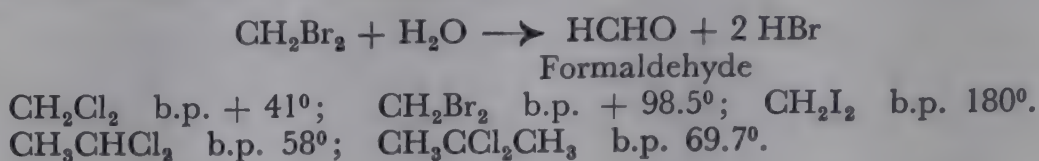
The dihalogen derivatives, particularly those which have the halogen attached to a carbon atom not at the end of the chain, are unstable. By the loss of halogen hydride they easily decompose giving unsaturated halogen compounds:

¹ By "gem." derivatives (abbreviation for geminal, from Geminus = twin), is meant compounds in which the substituents are attached to the same carbon atom.



The dihalogen derivatives of methane are those most commonly prepared. Since they contain the methylene group in the molecule, they are called *methylene chloride*, CH_2Cl_2 , *methylene bromide*, CH_2Br_2 , and *methylene iodide*, CH_2I_2 . They can be used for the introduction of the methylene radical into other compounds. Methylene iodide, on account of its high specific gravity (3.33) is used in mineral analysis for the separation of minerals of unequal specific weight.

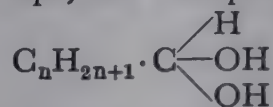
On heating with water, or weak alkalis (e.g. lead hydroxide) the methylene halides are hydrolysed to formaldehyde:



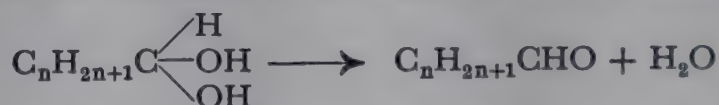
CHAPTER 9. THE DIVALENT OXYGEN FUNCTION: ALDEHYDES AND KETONES

Aldehydes

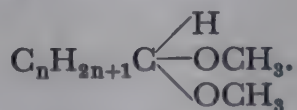
If the two hydrogen atoms at the end of the hydrocarbon chain are imagined to be replaced by hydroxyl groups, the compounds



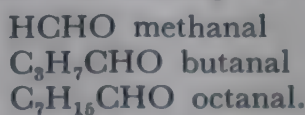
result — the “*gem.-glycols*”, or “*gem.-diols*”; they are, from the point of view of their chemical nature, the *hydrates of the aldehydes*, $C_nH_{2n+1}CHO$. These aldehyde hydrates are usually unstable in the free state. In experiments in which they might be isolated, the aldehyde itself is almost always obtained:



On the other hand, derivatives of them, the *acetals*, are known. These differ from the aldehyde hydrates in having two organic radicals in place of the hydrogen atoms of the hydroxyl groups:



Aldehydes are therefore derivatives of hydrocarbons which have the group —CHO at one end of the chain. The name is derived from “*alcohol dehydrogenatus*”, which itself signifies the fact that aldehydes are derived from alcohols by removal of hydrogen. Usually the various aldehydes are named from the carboxylic acids with the same number of carbon atoms. Thus one speaks of acetaldehyde, CH_3CHO , butyraldehyde, C_3H_7CHO , caproaldehyde, $C_5H_{11}CHO$, etc. The Geneva nomenclature prescribes the ending -al to signify aldehydic character:



METHODS OF FORMATION: 1. Quite the most important and most useful method of preparing the aldehydes is by the *regulated oxidation of primary alcohols*:



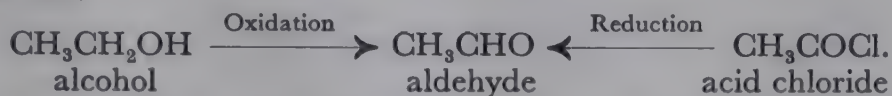
As an oxidizing agent atmospheric oxygen may be used in the presence of a catalyst (platinum, copper). In the laboratory, chromic acid, or manganese dioxide and sulphuric acid are chiefly used, the aldehyde being rapidly separated from the reacting mixture to protect it from further oxidation. The observation that an alcohol may be oxidized to an aldehyde without the presence of oxygen at all is of theoretical interest. Thus, if an alcohol is treated with a substance which can take up hydrogen, such as palladium, an aldehyde is formed (Wieland). This is a definite "dehydrogenation":



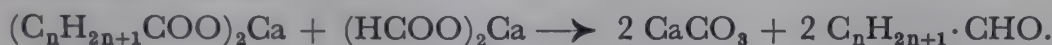
2. *Acid chlorides* can be smoothly reduced to aldehydes by treatment with hydrogen and palladium (Rosenmund):



This method of formation, together with the synthesis of aldehydes by the oxidation of primary alcohols, is conclusive proof of the constitution of the aldehydes. The two processes show that the aldehyde is intermediate in its state of oxidation between an alcohol and a carboxylic acid. Its constitutional formula must therefore be:



3. The *carboxylic acids* may be reduced to aldehydes by distilling their calcium salts with calcium formate:



According to Sabatier, a similar reaction takes place if the mixed vapours of the free carboxylic acid and formic acid are passed at 300–330° over catalysts (e.g. titanium oxide):



Moreover, if the vapour of the carboxylic acid is passed over zinc dust (300°) reduction often occurs to the corresponding aldehyde (Mailhe).

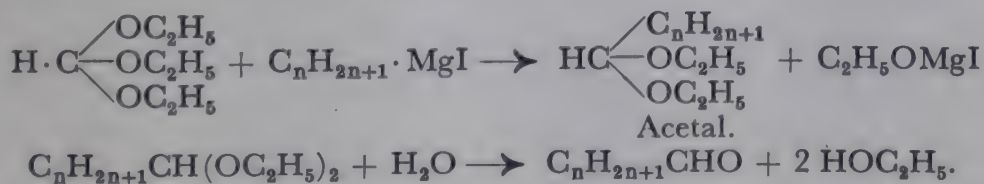
4. The preparation of aldehydes from gem.-dihalogen compounds is not very important, owing to the difficulty of obtaining such compounds. It has already been pointed out that methylene bromide gives formaldehyde on hydrolysis:



5. Another useful synthesis of aldehydes is the action of one molecule of *alkylmagnesium salt on a formic ester*, or orthoformic ester:



In the case of orthoformic ester acetals are first formed, but are hydrolysed to the free aldehydes by dilute acids:



PHYSICAL PROPERTIES. Formaldehyde is a gas at ordinary temperatures with a pungent, unpleasant smell. The higher homologues are liquids. With increasing length of the carbon chain their smell becomes more and more fruity, so that

some of them (e.g. those with nine and ten carbon atoms) are used in perfumery. The aldehyde group is a smell-producing, or *osmophoric* group.

The great reactivity of the aldehydes causes them to be unstable. Most of them change rapidly, and cannot be kept for an unlimited period:

		m.p.	b.p.
HCHO	Formaldehyde	— 92°	— 21°
CH ₃ CHO	Acetaldehyde	— 120°	+ 20.8°
C ₂ H ₅ CHO	Propionaldehyde		49°
C ₃ H ₇ CHO	<i>n</i> -Butyraldehyde		73°
C ₄ H ₉ CHO	<i>n</i> -Valeraldehyde		102°
C ₅ H ₁₁ CHO	<i>n</i> -Caproic aldehyde		128°
C ₆ H ₁₃ CHO	<i>n</i> -Heptoic aldehyde		155°
C ₇ H ₁₅ CHO	<i>n</i> -Caprylic aldehyde		b.p. ₉ 60–61°
C ₈ H ₁₇ CHO	<i>n</i> -Pelargonic aldehyde		b.p. ₁₃ 80–82°
C ₉ H ₁₉ CHO	<i>n</i> -Capric aldehyde		207–209°
C ₁₅ H ₃₁ CHO	Palmitic aldehyde	+ 34°	b.p. ₂₉ 200–201°
C ₁₇ H ₃₅ CHO	Stearic aldehyde	+ 63.5°	b.p. ₂₂ 212–213°

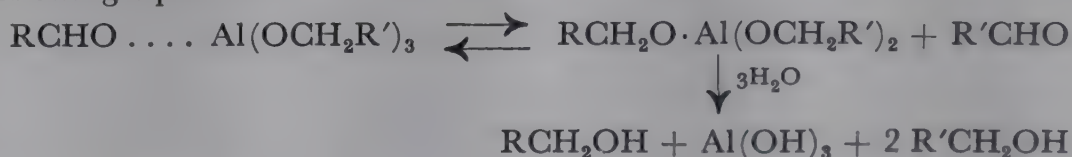
CHEMICAL REACTIONS OF THE ALDEHYDES: Many saturated aliphatic and aromatic aldehydes, e.g. *n*-dodecyl aldehyde, and benzaldehyde, split off carbon monoxide on exposure to ultra-violet light, and give hydrocarbons.

The reactive part of the aldehyde molecule is centred in the carbon-oxygen linking, the carbonyl group $>C=O$. Like other systems of “double bonds”, addition can take place across it. The following may be mentioned as examples of addition reactions:

(a) *Addition of hydrogen:* This occurs with nascent, or catalytically activated (Pt, Ni) hydrogen, and leads to primary alcohols:

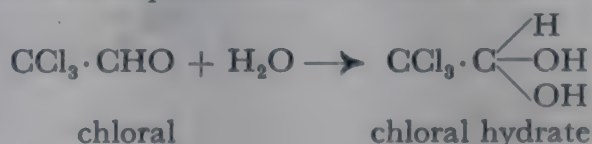


More recently use has been made of the Meerwein-Ponndorf method for the reduction of aldehydes (and ketones). It consists in the action of aluminium alcoholates on the carbonyl compounds. Addition products are first formed, which then break down according to the following equation:

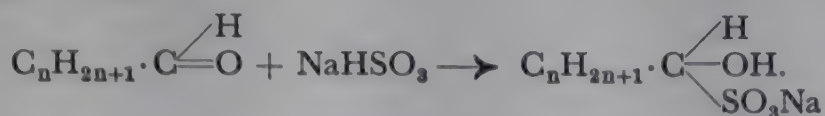


The reaction is reversible, i.e. the alcohol combined with the aluminium in the alcoholate can be oxidized to the carbonyl compound if a large excess of an aldehyde or ketone is used. The rate with which the equilibrium is attained depends primarily on the redox potential of the substances to the left and to the right side of the arrows. This method of reduction has the advantage that other reducible groups (carbon double bonds, etc.) are not attacked.

(b) *Addition of water* to aldehydes probably takes place in most cases in aqueous solution (often quantitatively), which may be concluded from the fact that aqueous solutions of aldehydes usually show only a slight absorption, or no absorption at all, of ultra-violet light, whereas, if a carbonyl group were present, the absorption would be considerable. The aldehyde hydrates are, however, usually too unstable to enable them to be isolated. Only in a few cases, e.g. *chloral*, can the hydrates be separated in the solid form:

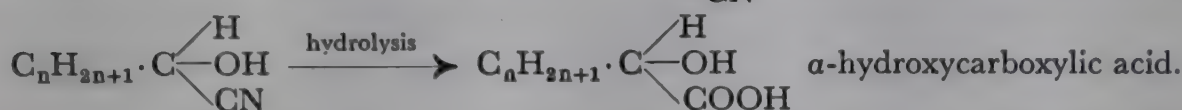
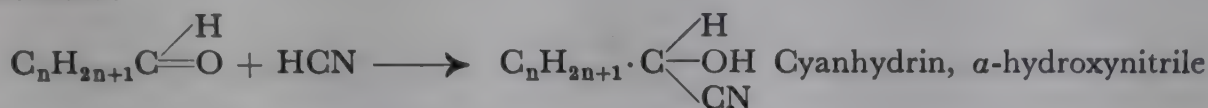


(c) Important products are obtained by the *addition of sodium bisulphite* to aldehydes. They are usually well-crystallized, difficultly soluble precipitates, and can be broken down into the aldehydes again by dilute acids and alkalis. They are therefore used for the separation of aldehydes from mixtures and for their isolation in a pure state:

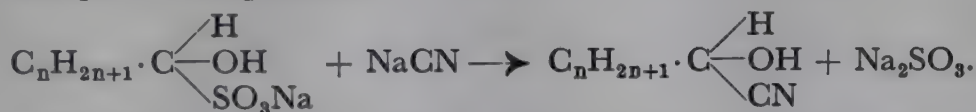


The bisulphite addition compounds are usually regarded nowadays as α -hydroxysulphonic acids.

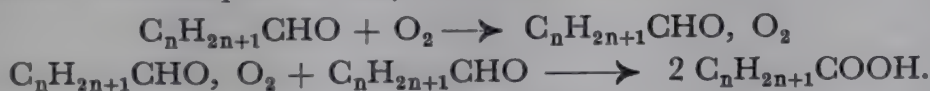
(d) *Hydrocyanic acid* also adds on easily to aldehydes, the addition of small amounts of ammonia or organic bases (alkylamines, quinoline, piperidine) often accelerating the reaction considerably. In this way the "cyanhydrins", or nitriles of the α -hydroxy-acids are produced. They are useful starting products for various syntheses:



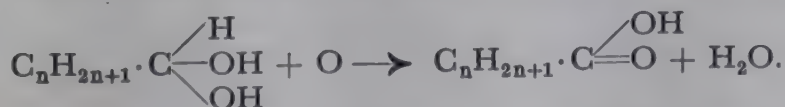
These compounds can also be obtained by the action of sodium cyanide on the aldehyde bisulphite compounds:



The aldehydes are readily acted upon by *oxidizing agents*. Many of them are oxidized on standing in the air; they are *autoxidizable*. They take up oxygen first in the molecular form, thus yielding molecular oxides (or per-acids?) which, however, easily give up half their oxygen to another aldehyde molecule, being themselves converted into simple carboxylic acids:



In aqueous solution the mechanism of the oxidation is usually different, being in the nature of a dehydrogenation. An acceptor, e.g. oxygen, can unite directly with the two active hydrogen atoms of the aldehyde hydrate. In this case the entrance of oxygen into the aldehyde molecule is not necessary for the oxidation:

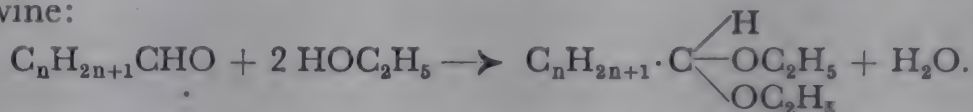


It is therefore possible to oxidize aldehydes to carboxylic acids without oxygen, with the aid of other hydrogen acceptors (e.g. quinone, Ch. 45).

Many salts of heavy metals, such as those of silver and gold, act as oxidizing agents for aliphatic aldehydes. Ammoniacal silver solutions and gold salts are reduced to the metals on warming with aldehydes, and cuprous oxide is precipitated from Fehling's solution. Hence, these reactions serve for the detection of aldehydes.

Another group of reactions of the aldehydes comprises those in which the carbonyl oxygen is replaced by other atoms or groups:

(a) The aldehydes react with alcohols in the presence of small quantities of anhydrous mineral acids or toluenesulphonic acid forming *acetals*. These are the alkyl ethers of the aldehyde hydrates. They are quite stable with respect to alkalis, but they are readily hydrolysed by aqueous mineral acids to the aldehydes. They have a pleasant flower-like smell. They are often found as by-products in the oxidation of alcohols, and are also formed, for example, in the ageing of wine:



The acetals play a great part in preparative chemistry. They contain a "protected" aldehyde group, and can, for example, be substituted by halogens, and thus be used for further syntheses of aldehyde derivatives.

Many anhydrous aldehydes react on mixing directly with alcohols, forming in an exothermic reaction addition compounds, which must be formulated as hemiacetals:

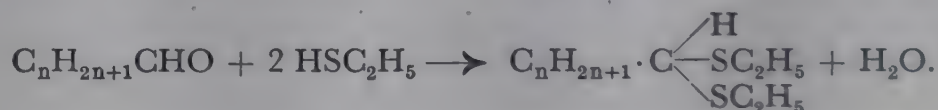


They are rather unstable, and are broken down on heating. From the absorption spectra of aldehydes in alcoholic solutions it may be shown that the alcohols have combined with the aldehydes, with removal of the C=O group, forming hemiacetals.

The formation of such hemiacetals is responsible for the origin of certain quantities of esters along with the aldehydes when alcohols are oxidized with bichromate for example. These esters are formed by the oxidation of hemiacetals that were primarily formed:



(b) Aldehydes combine with mercaptans as do alcohols, forming *mercaptals*, substances with an unpleasant smell, which are very stable towards acids and alkalis:

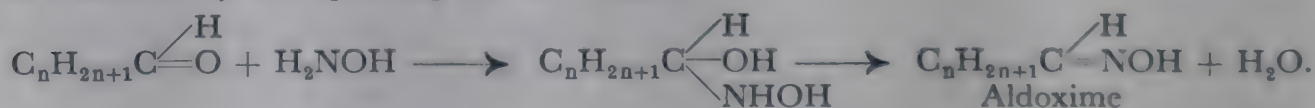


(c) The reactions of the aldehydes with some *nitrogen-containing reagents*, such as hydroxylamine, hydrazine, phenylhydrazine, and semicarbazide, are very important. Difficultly soluble, crystalline derivatives are often obtained from these reactions, which may be used for the characterization, and isolation of aldehydes from mixtures, and, since they can be decomposed into their components again, for the purification of aldehydes.

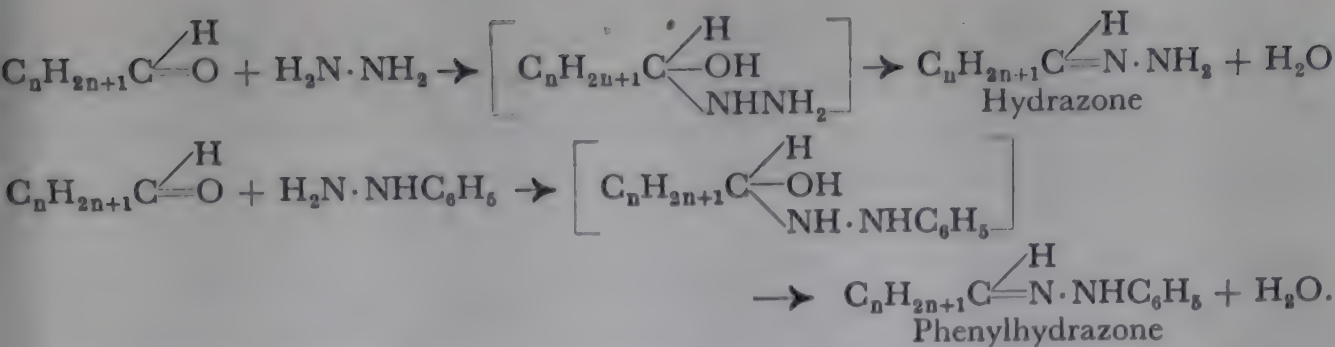
The reaction with hydroxylamine, NH_2OH , gives *aldoximes*:



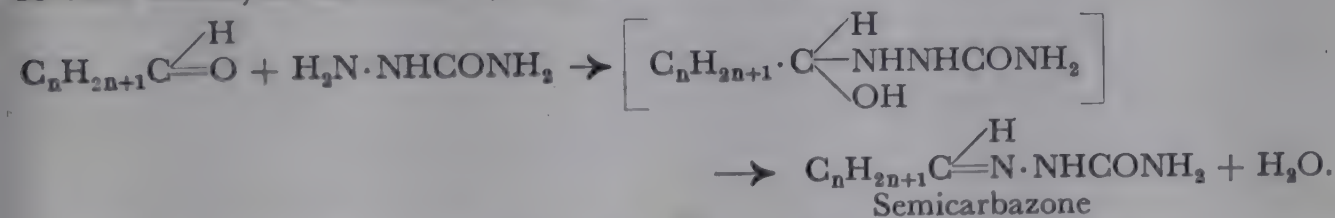
It is, however, probable that the reaction takes place in two stages, and the primary process is an addition of the hydroxylamine to the carbonyl group, which is followed by the splitting off of water:



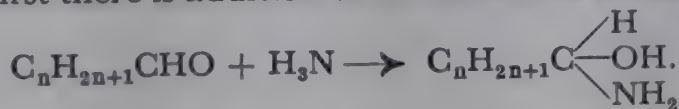
Aldehydes and hydrazine form, in a similar way, *hydrazones*. If phenylhydrazine is used, *phenylhydrazones* are produced:



The very reactive substance semicarbazide, $\text{H}_2\text{N}\cdot\text{NH}\cdot\text{CO}\cdot\text{NH}_2$ (and thiosemicarbazide, $\text{H}_2\text{NNHCSNH}_2$) is also often used for the preparation of difficultly soluble aldehyde derivatives, called *semicarbazones*:



The reactions between ammonia, and the aliphatic amines, with aldehydes are very similar. First there is addition of the ammonia across the carbonyl group:



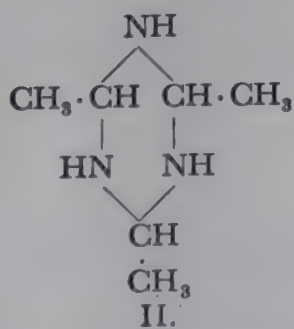
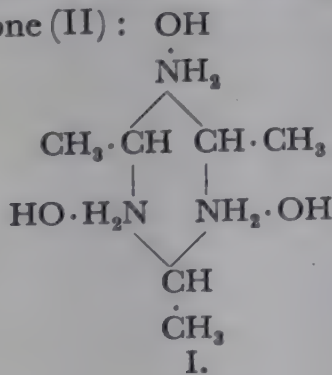
These *aldehyde ammonias*, however, are stable in only a few cases, e.g. trichloro-

acetaldehyde ammonia, $\text{CCl}_3\text{C} \begin{array}{l} \text{H} \\ \text{OH} \\ \text{NH}_2 \end{array}$, is known, as are also the alkyl-amino-

methanols obtained by the action of primary and secondary amines on formaldehyde:



The simpler aldehyde ammonias, e.g. that of acetaldehyde and ammonia, rapidly polymerize to trimolecular products (I) and lose water in a desiccator over concentrated sulphuric acid. The most probable formula for the oxygen-free compounds is a cyclic one (II):



Trimethyltrimethylenetriamine.

The aldehyde ammonias, from which the aldehydes can be regenerated, are often used for the purification of the latter.

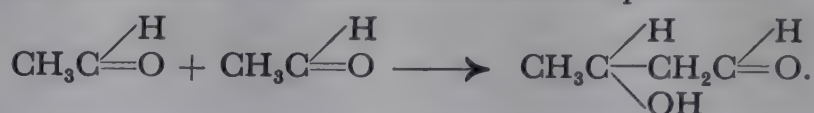
The reactivity of the aldehydes is also shown by their great *tendency to polymerize*. This polymerization can take place in different ways, according to the nature of the aldehyde, and that of the polymerizing reagent.

Some of the lower aldehydes (formaldehyde, acetaldehyde) polymerize under

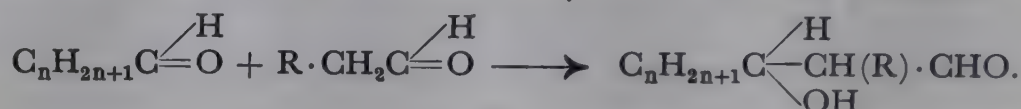
the influence of small amounts of mineral acids, to *trimolecular* compounds, which are not reducing agents. Their stability towards oxidizing agents shows that the aldehyde group is masked. They have a cyclic structure and are formed in the following way:



A much more general phenomenon is the “*aldol condensation*” of aldehydes, which takes place under the influence of small amounts of alkalis (alkali bicarbonates, alkali carbonates, alkali acetates, dilute alkali hydroxides, and alcoholates). A hydrogen atom of the carbon adjacent to the aldehyde group adds on to the oxygen of another aldehyde molecule, and the two aldehyde molecules link up by the carbon atoms to form a dimolecular product:



Obviously the reaction can only occur with those aldehydes which have at least one atom of hydrogen on the carbon atom adjacent to the aldehyde group. It can, however, also occur between aldehydes of different structure:

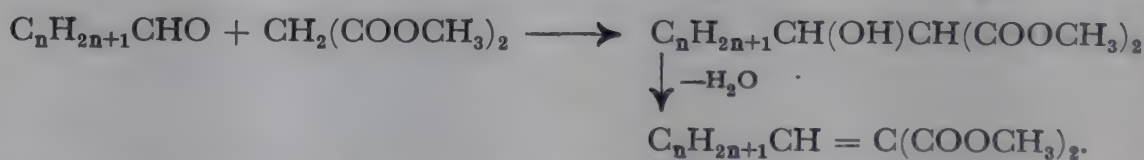


Often the hydroxy-aldehyde thus formed is further changed during the course of the reaction. It decomposes into water and an unsaturated aldehyde, for the synthesis of which this process provides a convenient method:



Similar processes as those involved in the aldol condensation take place when aldehydes react with compounds containing reactive methylene groups. By reactive (or “acid”) methylene groups is understood those of which the hydrogen is rendered mobile by the proximity of certain groups; such “activating” groups are, for example, $\text{C} = \text{O}$, $\text{C} \equiv \text{N}$, and others.

Aldehydes condense with such methylene compounds according to the scheme:



Substances capable of removing water (e.g. hydrogen chloride), or alkalis (amines) will act as condensing agents. The reaction is very useful for the synthesis of unsaturated compounds.

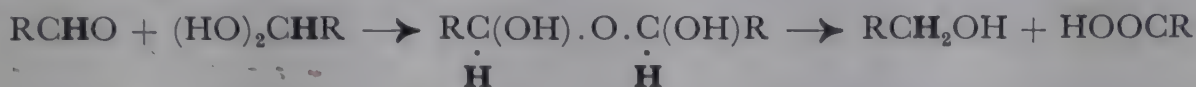
Some aldehydes undergo a peculiar change when treated with alkalis. An intermolecular displacement of oxygen occurs, one molecule of aldehyde being reduced at the expense of another, which is oxidized to an acid:



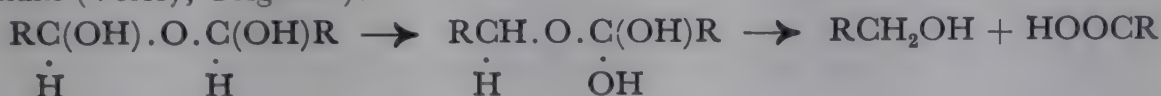
This “*disproportionation*” (or “*dismutation*”) is specially characteristic for aromatic aldehydes, and often proceeds so smoothly with these that it can be used for the preparation of certain aromatic alcohols and acids. In the aliphatic series

the reaction is given for example by formaldehyde and acetaldehyde. It is probable that it plays an important part in some biological processes (see, for example, alcoholic fermentation). The simultaneous formation of alcohols and carboxylic acids from aldehydes was discovered by Cannizzaro, and the reaction is named after him, Cannizzaro's reaction.

As regards the course of the Cannizzaro reaction of aldehydes it may be assumed, according to Meerwein and Schmidt, that 1 molecule of aldehyde and 1 molecule of aldehyde hydrate combine to form a compound of a hemiacetal type, which then decomposes according to the following scheme:

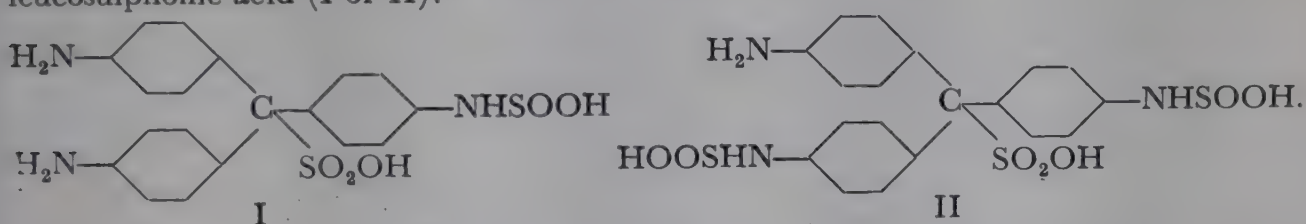


According to Bonhoeffer the course of the Cannizzaro reaction in heavy water (see Ch. 67, section 2) also supports this mechanism. The intermediate hemiacetal compound probably undergoes a rearrangement preliminary to cleavage as indicated by the following formulæ (Verley, Grignard):

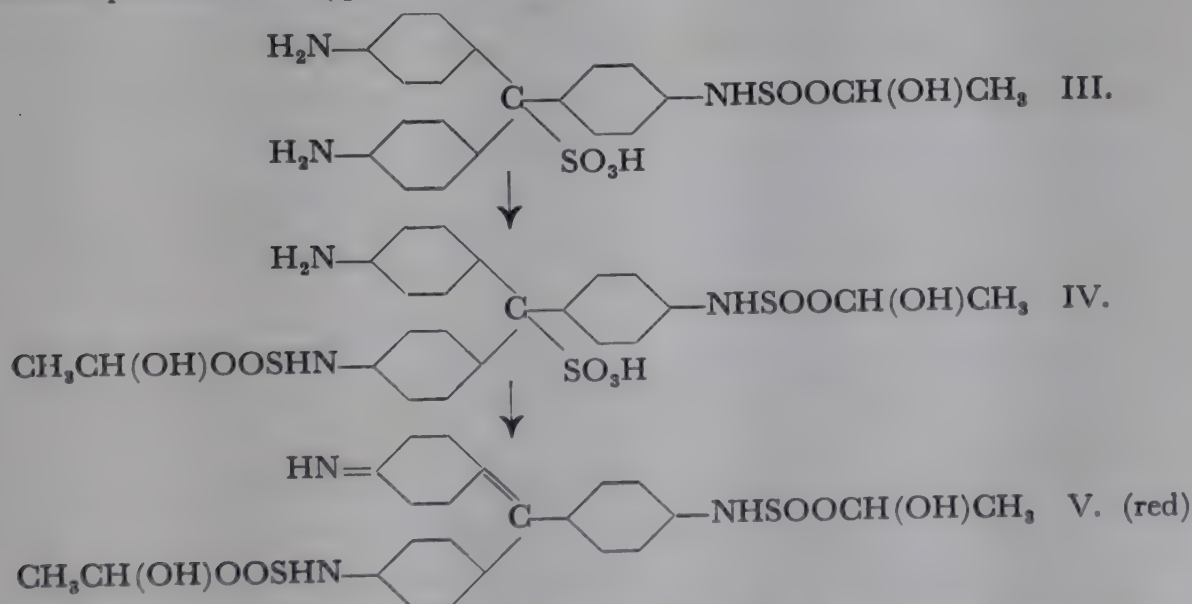


For the detection and characterization of aliphatic aldehydes, use is often made of their bisulphite compounds, their oximes, semicarbazones, and phenylhydrazones, as well as of their property of reducing silver salts, and of turning *fuchsin-sulphurous acid* (Schiff's reagent) red (Caro).

The red dye, parafuchsin (see Ch. 48) is converted by sulphur dioxide into a colourless compound, which according to H. Wieland, is the N-sulphinic acid of parafuchsin-leucosulphonic acid (I or II):



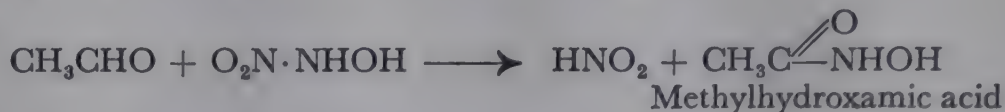
From these, on addition of an aldehyde, the compounds III and IV are formed, which are also colourless. The latter then loses the sulphinic acid group attached to the C-atom to produce a red (quinonoid) dye, V:



After some time, compound V decomposes into acetaldehyde-bisulphite and fuchsin-sulphurous acid, and decolorization of the liquid again occurs.

The reaction with Schiff's reagent is very sensitive, but is not specific for aldehydes, as it gives positive results also with certain ketones. Moreover, oxidizing agents (e.g. cupric salts) also turn Schiff's reagent red.

Another test for the detection of aldehydes is due to Angeli and Rimini. It depends on the fact that aldehydes combine with nitrohydroxylamine, $\text{O}_2\text{N}\cdot\text{NHOH}$ (also $\text{C}_6\text{H}_5\text{SO}_2\text{NHOH}$) to give *alkylhydroxamic acids*, which can easily be recognized by the intense blood-red colour they give with iron salts:

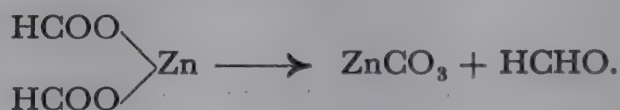


Formaldehyde, methanal, HCHO .¹ Traces of formaldehyde are formed in the incomplete combustion of many organic substances, e.g. coal, wood, sugar, etc. Formaldehyde is therefore always present in smoke and soot, and occurs in small amounts in the atmosphere. The disinfecting effect of smoke, which is made use of in smoking meat, is at least partially due to this. It is of theoretical interest to note that the simplest hydrocarbon, methane, also gives formaldehyde on incomplete combustion.

Technically the compound is obtained exclusively by the *oxidation of methyl alcohol*. The oxidizing agent is atmospheric oxygen. The mixture of methyl alcohol vapour and air is passed over heated contact catalysts; in place of platinum which was first recommended for this purpose, heated copper, or red-hot alumina or charcoal are now used:

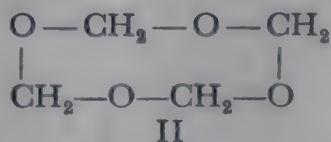
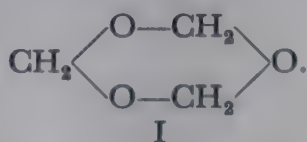


It is also possible to prepare formaldehyde by the reduction of carbon monoxide with hydrogen, or from water gas, $\text{CO} + \text{H}_2$. The method has, however, not yet been used technically, and the same applies to the dry distillation of zinc formate which gives a good yield of formaldehyde:



Formaldehyde is a gas at ordinary temperatures (b.p. -21°) and has a pungent smell. In commerce it occurs as a 40 per cent aqueous solution (formalin), and various solid polymers are also used.

Formaldehyde shows a remarkable tendency to polymerize. Its most stable, and best investigated polymeride is *α -trioxymethylene*, a crystalline compound, which volatilizes without decomposition, shows no reducing properties, and has the molecular formula $(\text{CH}_2\text{O})_3$. These properties are best explained by giving the substance the cyclic structure (I).



A crystalline "*tetraoxymethylene*" is also known, which probably has the formula II. It has properties analogous to trioxymethylene.

By concentrating aqueous solutions of formaldehyde other polymeric modifications, the so-called "*poly-oxymethylenes*", (or "*paraformaldehyde*"), are formed.

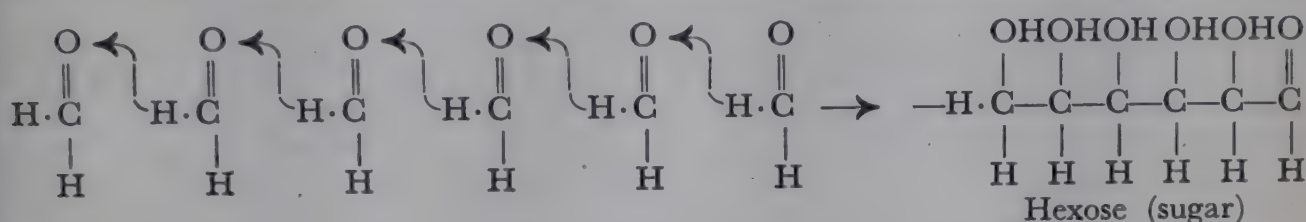
¹ J. FREDERIC WALKER, *Formaldehyde*, New York, (1945).

According to the work of H. Staudinger, this is a mixture of substances of various degrees of polymerization, some of which have been separated. In these polymeric homologous compounds the linking of the individual formaldehyde radicals takes place through the oxygen atoms, and the ends of the chain are saturated by taking up the elements of water, so that they can be referred to as "poly-oxy-methylene dihydrates". Their structure corresponds to formula III, and their formation can be supposed to be due to the elimination of water from hydrated formaldehyde molecules:



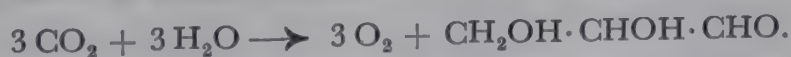
The poly-oxy-methylenes reduce Fehling's solution, and break down fairly easily (e.g. by heating) into monomeric formaldehyde. According to their degree of polymerization they may be soluble or insoluble in water, volatile or involatile. The insoluble products appear to consist of 100 or more molecules of CH_2O .

The most interesting type of polymerization that formaldehyde undergoes is that which occurs under the influence of weak alkalis (e.g. milk of lime). O. Loew has found that a mixture of different sugars is thus formed, which have been produced from the aldehyde through a chain of aldol condensations (see p. 342).



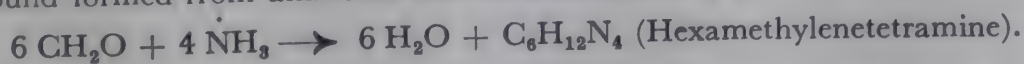
E. Fischer has isolated a compound (α -acrose) in the pure state from the sugar syrup, and has converted this substance into other natural sugars, thus bringing about the total synthesis of these natural carbohydrates (see also sugars).

The above-described process of polymerization of formaldehyde to sugars was formerly considered to be also of physiological significance, as it was assumed that the carbohydrates are formed in green plants in an analogous manner during the process of assimilation (A. von Baeyer, R. Willstätter and A. Stoll, O. Warburg). To-day, however, the view accepted by some investigators is that formaldehyde is not the initial product of assimilation, or at most a by-product in that process. It is assumed that D-glyceraldehyde is the first carbohydrate synthesized by the plant, and that it is formed from carbon dioxide and water:



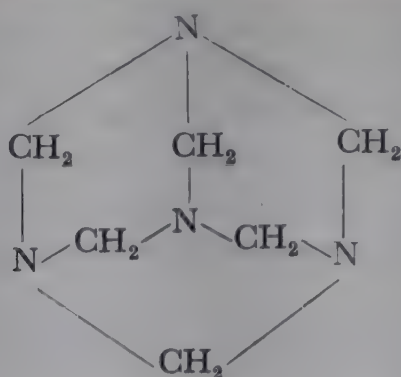
The other carbohydrates are formed from glyceraldehyde by rearrangements and condensations.

The strong disinfecting properties and the capacity of combining with proteins and many other substances to give difficultly soluble compounds of complex composition, have given great importance to formaldehyde in industry. In medicine it is used, and for the disinfection of rooms as an antiseptic. Numerous condensation products of formaldehyde with amino-compounds, proteins, phenols, etc., which yield formaldehyde on decomposition, are used for internal disinfection. Among them, *hexamethylenetetramine*¹, or urotropine, a compound formed from ammonia and formaldehyde, is specially important:

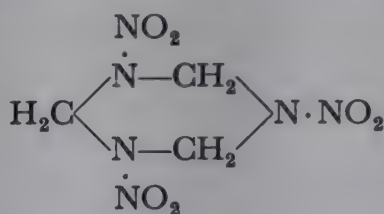


¹ JULIUS ALTPETER, *Das Hexamethylenetetramin und seine Verwendung*, Halle, (1931).

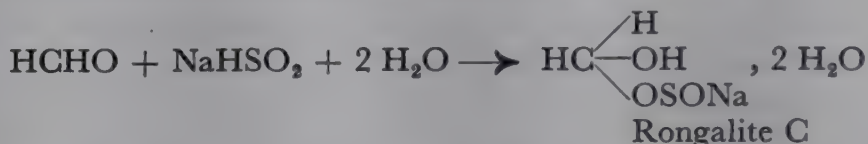
The constitution of urotropine is probably as follows:



The compound forms colourless crystals, is easily soluble in water, and tastes sweet. It is used as an internal disinfectant, especially for the urinary system, and is also employed in the treatment of gout, and infectious diseases. In recent times an explosive, *cyclo-trimethylene-trinitramine* ("hexogen") has been produced by nitrating urotropine:



Condensation products of formaldehyde with phenols are used as *synthetic resins* (bakelite), and those with phenol- and naphthalenesulphonic acids as synthetic *tannins* (neradol). From formaldehyde and casein plastics similar to horn are prepared, and are used as *substitutes for natural horn*, tortoiseshell, and ivory (galalith, artificial horn). Leather is often treated with formaldehyde before tanning. The compound is also used in the synthesis of many dyes (fuchsin, acridine, and pyronine dyes). Finally, a compound of formaldehyde and sodium hydrosulphite, *sodium formaldehyde-sulphoxylate* (rongalite C, hyraldite) is used as a reducing agent in the decolorization of vat dyes. In its preparation, e.g. from formaldehyde and sodium hydrosulphite in alkaline solution, the sodium sulfoxylate formed from the sodium hydrosulphite adds on to the aldehyde:

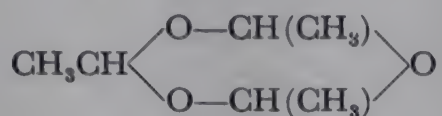


Acetaldehyde, ethanal. *Acetaldehyde* is found, chiefly as acetal, in small quantities in the head fraction of the distillate from alcoholic fermentation, and is here produced by oxidation from alcohol. This, the second member of the series of aldehydes, also has considerable biological importance, since acetaldehyde, as has been pointed out, is an intermediate product in the alcoholic fermentation of various sugars (see the section on alcoholic fermentation). It may also play a part in the carbohydrate metabolism of the animal cell. It is occasionally found in urine.

Two processes are in use for the technical preparation of acetaldehyde. One depends on the oxidation of ethyl alcohol with dichromate and sulphuric acid, or better with air, in which case heated metals are used as catalysts. More recently most of this substance has been produced by the addition of water to acetylene (see p. 70) in the presence of mercury salts.

Acetaldehyde is a mobile liquid with a pungent, stupefying smell. It boils at 21°. It is easily soluble in water, and shows a great tendency to polymerize. A drop of concentrated sulphuric acid added to the anhydrous aldehyde causes it to polymerize to the trimeric *paraldehyde*, $(\text{CH}_3\text{CHO})_3$. The reaction is so violent

that it may cause the liquid to boil. At lower temperatures, and also with small quantities of sulphuric acid as polymerizing agent, another polymeric form, *metaldehyde*, is produced. Paraldehyde is a liquid (b.p. 124°) and metaldehyde is a solid. Both polymers are unable to reduce ammoniacal silver nitrate, and do not resinify when treated with alkalis. They therefore contain no free aldehydic groups. They can, however, be fairly easily reconverted slowly into the monomolecular acetaldehyde, for example, by distilling with dilute sulphuric acid, or even by heating with water. These properties, as well as the results of the cryoscopic determinations of their molecular weights, show that both polymers most probably have ring formulæ, e.g. for paraldehyde:



Paraldehyde is used in medicine as a hypnotic. Metaldehyde is used as a solid fuel ("meta"). Acetaldehyde itself has been used in the preparation of silver mirrors, and is an important intermediate in the manufacture of acetic acid.

Higher aldehydes. The aldehyde with seven carbon atoms, *OENANTHAL* $\text{CH}_3(\text{CH}_2)_5\text{CHO}$, is readily obtained by the distillation of castor oil under reduced pressure. Its formation is due to the decomposition of ricinoleic acid.

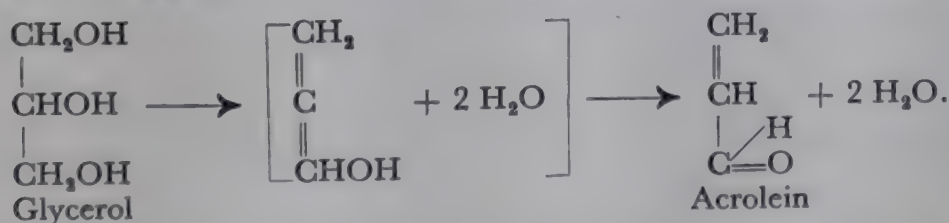
Oenanthal is a liquid with a strong smell. Heptyl alcohol, $(\text{CH}_3)(\text{CH}_2)_5\text{CH}_2\text{OH}$ and heptic acid, $\text{CH}_3(\text{CH}_2)_5\text{COOH}$, which are both used in perfumery, are both made from it on a commercial scale. *Heptyne* is also obtained from it as follows:



The sodium compound of heptyne combines with carbon dioxide to give heptyne-carboxylic acid, $\text{CH}_3(\text{CH}_2)_4\cdot\text{C}\equiv\text{C}\cdot\text{COOH}$, the methyl ester of which is an important perfume (artificial smell of violet leaves, Moureu).

CAPRYLIC ALDEHYDE, $\text{C}_7\text{H}_{15}\text{CHO}$, and **PELARGONIC ALDEHYDE**, $\text{C}_9\text{H}_{17}\text{CHO}$, are found in essential oils (citronella oil, rose oil, etc.). Their pleasant smell makes them of use in perfumery. The synthetically produced 3-methylnonyl aldehyde, $\text{CH}_3(\text{CH}_2)_5\text{CH}(\text{CH}_3)\text{CH}_2\cdot\text{CHO}$, 3-methyldodecyl aldehyde, $\text{CH}_3(\text{CH}_2)_8\text{CH}(\text{CH}_3)\text{CH}_2\text{CHO}$, undecyl aldehyde, $\text{CH}_3(\text{CH}_2)_9\text{CHO}$, and lauric aldehyde, $\text{CH}_3(\text{CH}_2)_{10}\text{CHO}$, serve the same purpose.

Unsaturated aldehydes. Acrolein. The simplest unsaturated aldehyde is acrolein, which is formed in small quantities in the distillation of fats, but is better prepared by heating glycerol with dehydrating agents (e.g. potassium bisulphate):



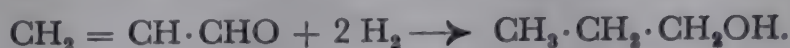
This unsaturated aldehyde is a clear liquid with an intolerable smell. It boils at 52°. Its unsaturated nature is shown by its great instability, and tendency to polymerize. According to Moureu, acrolein can, however, be preserved for much

longer periods by the addition of small quantities of other substances, themselves easily oxidizable, e.g. phenols, hydroquinone, etc.

The reactivity of acrolein makes it useful in various syntheses. Either the carbon-carbon double bond, or the carbon-oxygen double bond reacts according to the type of addendum. Thus, halogens, or halogen hydrides add on to the former, hydrocyanic acid to the latter:

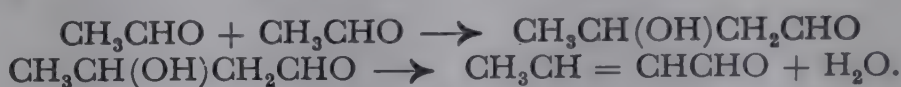


Hydrogen reduces both double bonds:



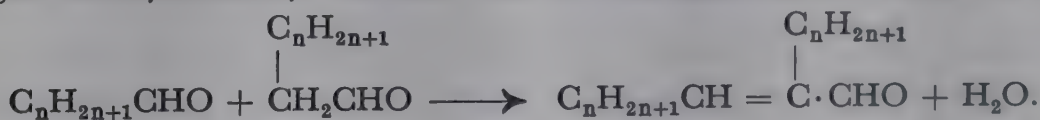
The reduction may also be conducted so as to lead to the formation of an intermediate product, allyl alcohol, $\text{CH}_2 = \text{CHCH}_2\text{OH}$.

Of the *higher unsaturated aldehydes*, those in which the double bond lies between the α - and β -carbon atoms can easily be obtained by a method previously described. It is the removal of water from two molecules of an aldehyde under the influence of dilute alkalis, carbonates, sodium acetate, or zinc chloride, the first stage of the reaction being an aldol condensation:



That the process takes this course can be proved from the fact that the unsaturated aldehyde produced (crotonaldehyde) can be oxidized to crotonic acid, $\text{CH}_3 \cdot \text{CH} = \text{CH} \cdot \text{COOH}$, of which the constitution is known by various methods.

Higher aldehydes always condense with the α - CH_2 -group, according to the scheme:

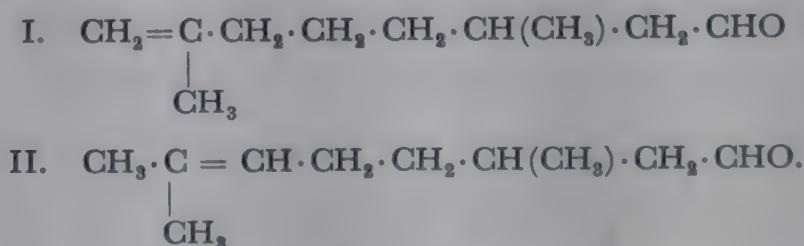


These unsaturated aldehydes are similar to acrolein in many chemical properties, and are to be considered as higher homologues of this substance.

Crotonaldehyde, $\text{CH}_3\text{CH} = \text{CH} \cdot \text{CHO}$, boils at 104° , and **tiglic aldehyde**,



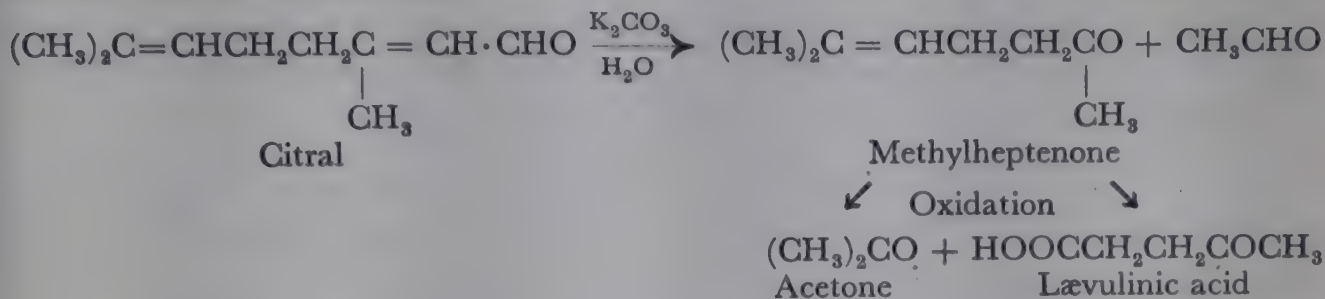
Citronellal is a naturally occurring, unsaturated aldehyde with ten carbon atoms. Its *d*-form is found in citronella oil, eucalyptus oil, and the oil of *Barosma pulchellum*, and the *l*-form in Java lemon oil. Two formulæ have been proposed for this substance (I and II). Possibly it is mixture of the two:



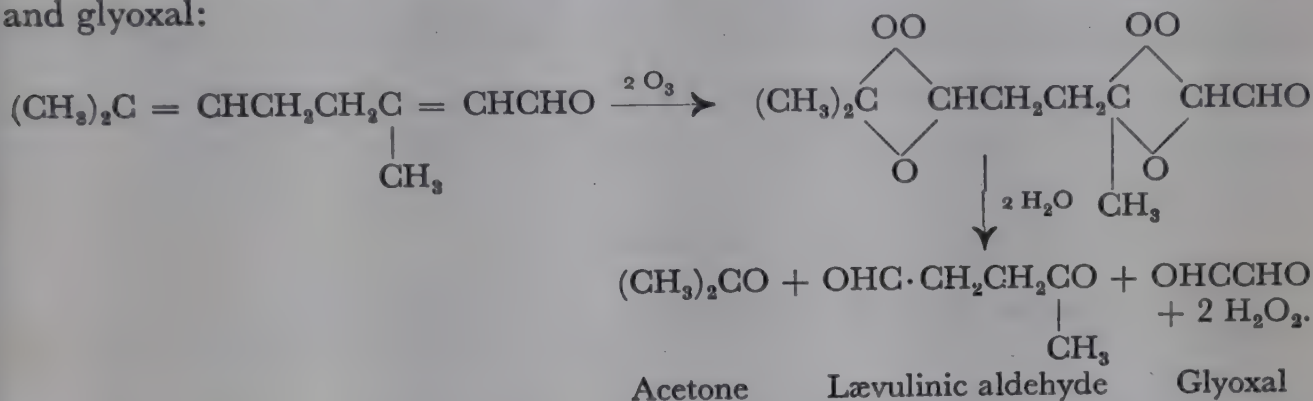
Citronellal boils at 202° , and has a strong, pleasant smell, which makes it of use in perfumery. Reduction of citronellal gives *citronellol* (see p. 109), and oxidation leads to different oxidation products according to the oxidation conditions used. From these products the constitution of citronellal can be arrived at.

Citral, an aldehyde with two double bonds, is of great importance. It is found in many essential oils, and particularly in verbena oil, lemongrass oil and in lemon oil. Its constitution is arrived at from its degradation (Barbier and Bouveault, Tiemann, Semmler, Harries), and has been verified by synthesis.

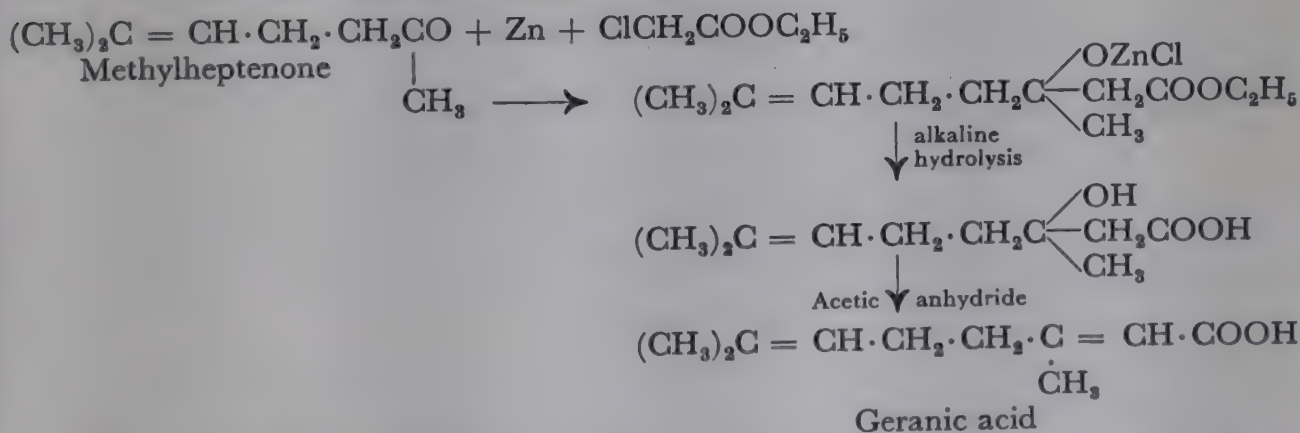
On heating with alkalis, citral gives acetaldehyde and methylheptenone. The constitution of the latter is known from the fact that it gives on oxidation acetone and lævulinic acid:



The action of ozone on citral gives a clear indication of the positions of the double bonds since the ozonide breaks down into acetone, lævulinic aldehyde, and glyoxal:

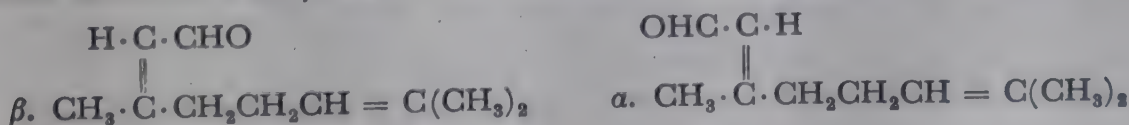


The *synthesis of citral* starts from synthetic methylheptenone, and proceeds through the following steps:



The calcium salt of geranic acid distilled with calcium formate gives citral.

For ethylenic compounds of the structure $\begin{array}{c} \text{X} \quad \quad \text{Z} \\ \diagdown \quad \diagup \\ \text{C}=\text{C} \\ \diagup \quad \diagdown \\ \text{Y} \quad \quad \text{R} \end{array}$ two possible geometrical isomerides may exist. The two corresponding forms of citral (α and β)



are known. The citral of commerce is a mixture of the two. On reduction, geraniol is chiefly formed. On the other hand, the two stereoisomeric alcohols geraniol and nerol (see p. 110) give citral on oxidation under suitable conditions. Geraniol gives chiefly α -citral, and nerol, β -citral.

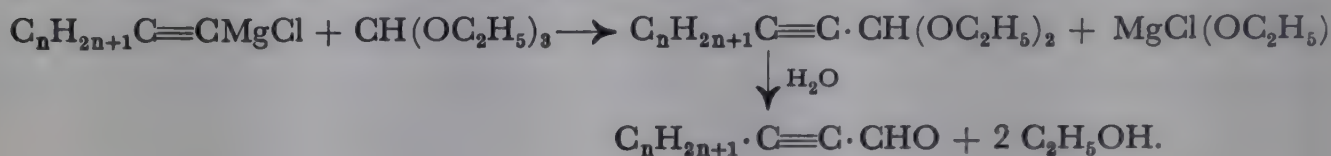
Citral is a yellowish oil with a strong odour of lemons. Its boiling point is 228° . It is used as a perfume, and as a starting material for the preparation of artificial violet scents (see ionones).

In violet leaves and in cucumbers a doubly unsaturated aldehyde with nine carbon atoms has been found, which has the constitution of nonadien-(2:6)-al-(1):



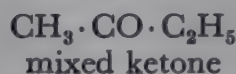
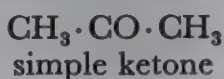
Several representatives of *aldehydes with a triple bond* are known. The simplest, PROPARGYL ALDEHYDE, $\text{CH} \equiv \text{C} \cdot \text{CHO}$ is a volatile liquid, of which the vapour irritates the mucous membrane like acrolein.

A general synthesis of aldehydes of the formula $\text{C}_n\text{H}_{2n+1}\text{C} \equiv \text{C} \cdot \text{CHO}$ is the action of acetylenemagnesium salts on orthoformic ester. The acetals thus formed give the acetylenic aldehydes on hydrolysis with dilute acids:

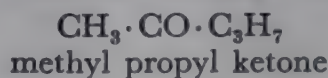
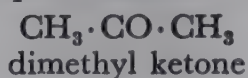


Ketones

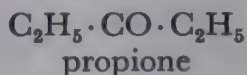
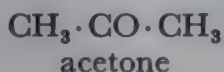
Ketones are compounds, in which the carbonyl group, $\text{C}=\text{O}$, is linked to two alkyl radicals. If the latter are identical the substance is a *simple ketone*; if they are different, the substance is referred to as a *mixed ketone*:



The name "*ketone*" is derived from that of the simplest member, acetone. Some ketones have common names. Otherwise, the names of the compounds are formed from the alkyl groups contained in them, with the ending "*ketone*", thus:



The names for symmetrical, simple ketones, may also be derived from the names of the acids, from which they are formed (together with water and carbon dioxide) when heated with a contact catalyst:



The Geneva nomenclature uses the ending —one to show that a compound is ketonic in nature:

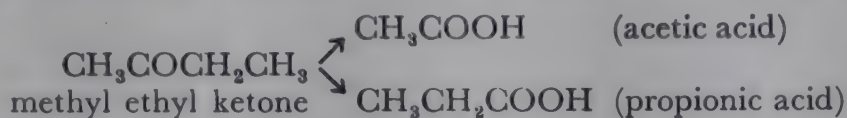


METHODS OF FORMATION: 1. The ketones are closely related to the aldehydes. Like the latter they contain a carbonyl group. It may therefore be predicted that they will enter into many of the reactions of aldehydes for which the carbonyl group is responsible. On the other hand, the fact that in ketones the carbonyl group is attached to *two* alkyl radicals, causes them to react somewhat differently in some cases. This is shown, for example, particularly in their behaviour towards oxidizing agents.

Just as aldehydes are obtained from primary alcohols, ketones are formed by the *oxidation of secondary alcohols*. This reaction provides at the same time a proof of their structure:

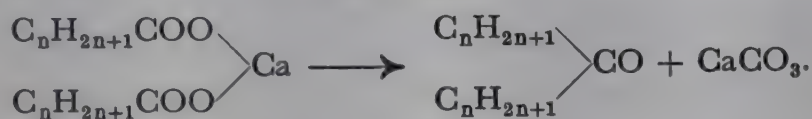


Whilst however, the aldehydes are very sensitive to further oxidation, and are thus converted into carboxylic acids with the same number of carbon atoms, ketones offer greater resistance to oxidation. When they are eventually oxidized by strong oxidizing agents (e.g. chromic acid mixture, potassium permanganate), fission between the carbonyl group and an adjacent alkyl radical occurs, so that an acid is formed which contains fewer carbon atoms than the ketone itself:

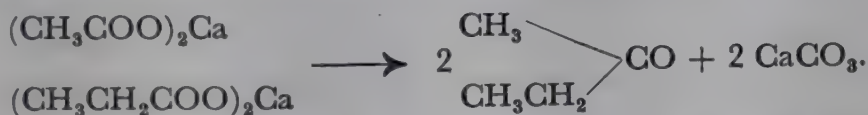


The greater stability of the ketones towards oxidizing agents is also shown by the fact that they will not reduce ammoniacal silver nitrate, gold salts, or Fehling's solution. In this respect they differ from the aldehydes.

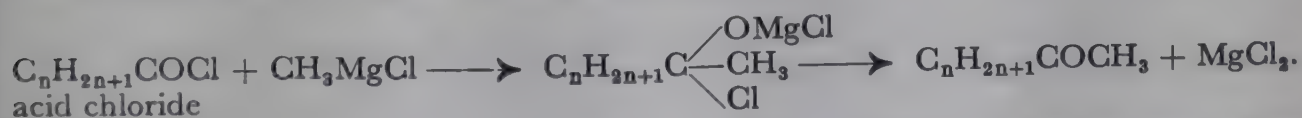
2. Ketones are formed by the *dry distillation of the calcium or barium salts of the carboxylic acids*, or by passing the vapour of the carboxylic acids over heated zinc oxide or heated thoria. This method of preparation corresponds to the formation of aldehydes from a mixture of the calcium salts of carboxylic acids and formic acid, or from a mixture of the free carboxylic acid and formic acid:



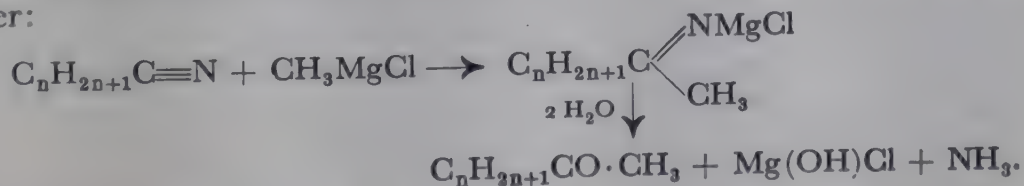
If mixtures of the calcium salts of two different carboxylic acids are used in this synthesis, unsymmetrical ketones are formed in addition to the symmetrical ones:



3. Carboxylic acids can also be converted into ketones through the *acid chlorides* and nitriles by allowing them to act upon Grignard reagents (or alkylzinc salts $\text{C}_n\text{H}_{2n+1}\text{ZnI}$ or organic cadmium compounds):

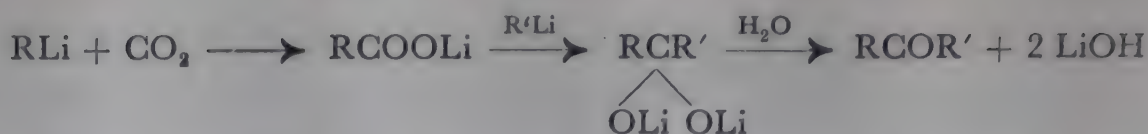


The alkylmagnesium salts add on to *nitriles* at first in a similar way. The magnesium salts of the ketimines thus formed are then hydrolysed by the addition of water:



This mechanism only holds, however, for those nitriles which contain the grouping $-\text{CH}_2\text{CN}$. In other cases the action of the Grignard reagent results frequently in the elimination of the CN-group, the alkyl radical entering in its place.

4. The recently discovered lithium alkyls may also be used in the synthesis of ketones. With dry carbon dioxide they react according to the scheme:



giving dilithium salts of the ketone hydrates, which break down on addition of water into ketones and lithium hydroxide (H. Gilman).

5. A very useful synthesis of ketones depends on the *condensation of esters of carboxylic acids with reactive methylene and methyl groups*. As a simple example of this kind the combination of two molecules of ethyl acetate to give acetoacetic ester, the ester of a β -ketocarboxylic acid, may be mentioned. The condensation takes place under the influence of sodium ethylate (see acetoacetic ester):



β -Ketocarboxylic acids decompose very easily on hydrolysis with dilute alkalis into carbon dioxide and ketones:



By suitably choosing the starting materials it is possible to synthesize almost any given ketone by this process.

PHYSICAL PROPERTIES. The lower ketones are mobile liquids, soluble in water, with a refreshing smell. The middle members are no longer soluble in water. Many of them smell flower-like, others have an unpleasant, rancid smell. The highest ketones are solid.

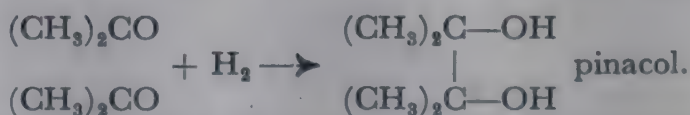
		b.p.	m.p.
Acetone	$(\text{CH}_3)_2\text{CO}$	57°	—93°
Diethyl ketone (propione)	$(\text{C}_2\text{H}_5)_2\text{CO}$	101°	—41.5°
<i>n</i> -Dipropyl ketone (butyrone)	$(\text{C}_3\text{H}_7)_2\text{CO}$	144°	—34°
<i>n</i> -Dibutyl ketone (valerone)	$(\text{C}_4\text{H}_9)_2\text{CO}$	187°	— 5.9°
<i>n</i> -Diamyl ketone (capronone)	$(\text{C}_5\text{H}_{11})_2\text{CO}$	227°	+ 15°
<i>n</i> -Dihexyl ketone (œnanthone)	$(\text{C}_6\text{H}_{13})_2\text{CO}$	264°	+ 30°
<i>n</i> -Dioctyl ketone (pelargone)	$(\text{C}_8\text{H}_{17})_2\text{CO}$		50°
Myristone	$(\text{C}_{13}\text{H}_{27})_2\text{CO}$		76°
Palmitone	$(\text{C}_{15}\text{H}_{31})_2\text{CO}$		83°
Stearone	$(\text{C}_{17}\text{H}_{35})_2\text{CO}$		88°

CHEMICAL PROPERTIES. Many of the chemical reactions of the ketones are perfectly analogous to those of the aldehydes. In a few cases, however, there are quantitative differences, the reactivity of the carbonyl group in ketones being somewhat less than that in aldehydes.

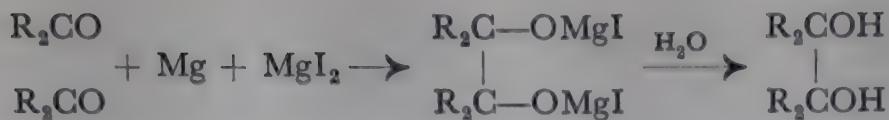
(a) By the *action of strong reducing agents* ketones are converted into secondary alcohols:



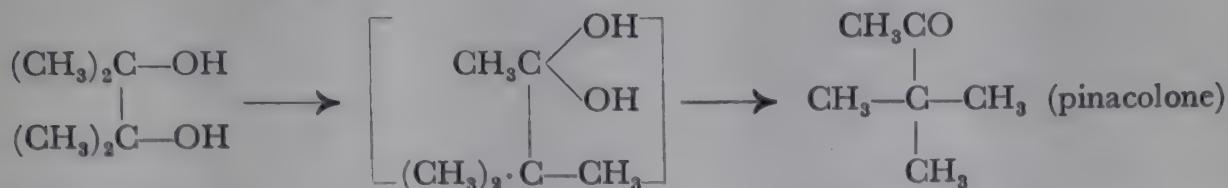
It is, however, also possible to carry out the reduction so that each molecule of ketone takes up only one atom of hydrogen. This is, for example, the case if the ketone is carefully acted upon by sodium, sodium amalgam, or magnesium amalgam, in strongly alkaline solution. The products are the *pinacols*, dihydric, di-tertiary alcohols, with adjacent hydroxyl groups. The reduction is called the *pinacol reduction*:



A peculiar reduction process for converting ketones into pinacols has been found in the action of magnesium and magnesium iodide on ketones. Certain Grignard reagents act in a similar manner (e.g. triphenylmethylmagnesium bromide). The course of the reaction is possibly as follows:

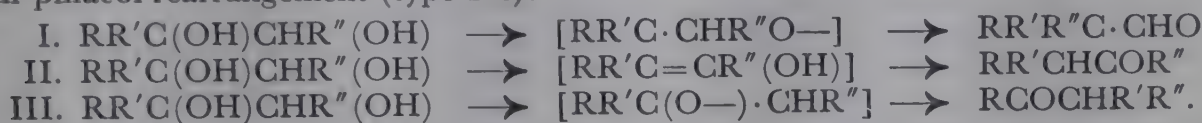


Pinacols undergo a peculiar rearrangement to new ketones when treated with concentrated sulphuric acid. The rearrangement leading to pinacolones is known as the "*pinacol rearrangement*":

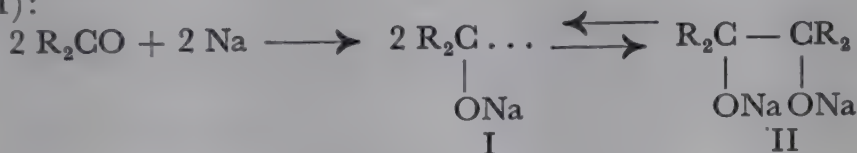


In the pinacolones, the ketonic group is attached to a tertiary carbon atom.

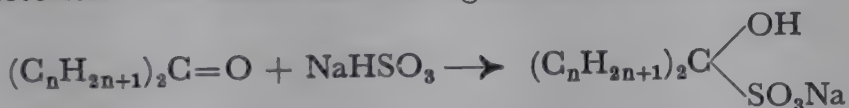
Rearrangements can also occur with the tertiary-secondary dihydric alcohols of the type $\text{RR}'\text{C}(\text{OH})\cdot\text{CHR}''(\text{OH})$ when treated with dehydrating agents. These transformations occur in different ways according to the nature of the substituents. The following types are recognized: semi-hydrobenzoin changes (type I), vinyl dehydration (type II), and semi-pinacol rearrangement (type III):



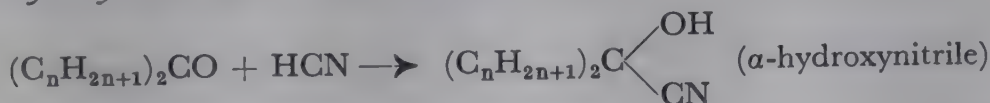
(b) By the action of sodium on ketones in the absence of air, coloured solutions are obtained, which contain, according to Schlenk, the so-called *metal ketyls*, i.e. radicals of the composition (I), which are in equilibrium with the dimeric sodium pinacolates (II):



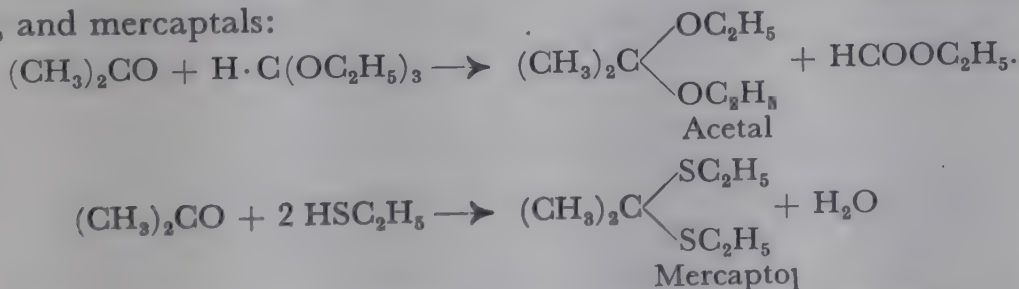
(c) *Sodium bisulphite* gives crystalline addition products with the majority of aliphatic ketones. The latter can be regenerated from them:



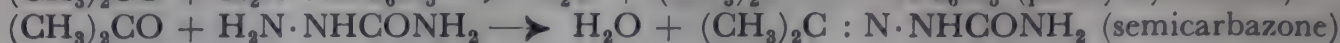
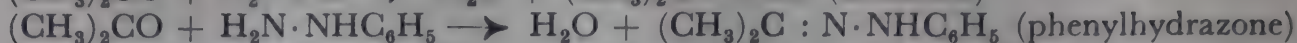
(d) *Hydrocyanic acid* also adds on to ketones:



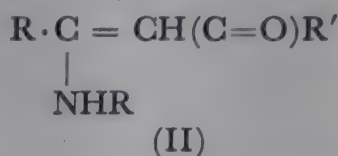
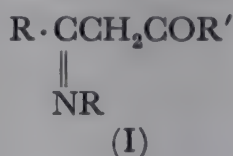
(e) With orthoformic esters in the presence of alcohols, and with thioalcohols, the ketones yield, in the presence of small amounts of anhydrous acids, *ketone-acetals* and *mercaptols* respectively. These are the analogues of the aldehyde-acetals, and mercaptals:



(f) The nitrogenous reagents, hydroxylamine, phenylhydrazine, semicarbazide, etc., give with ketones *oximes*, *phenylhydrazones*, and *semicarbazones*, respectively (see also p. 296):



(g) By the action of ammonia or amines on ketones, water is often readily split off, and the ketimides (I), which, however, are better regarded as enamines (II), are formed. The latter formulation is particularly supported by the strong optical exaltation which these compounds possess, and which indicates a conjugated system $\text{N}=\text{C}=\text{C}=\text{O}$ (K. v. Auwers).

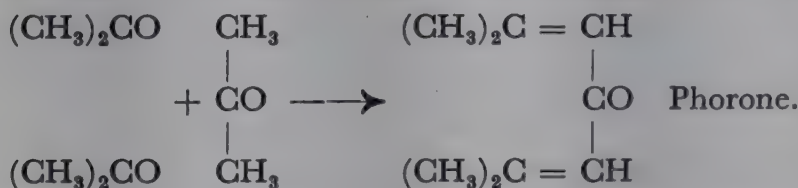


(h) Their outstanding capacity for polymerizing has been mentioned as one of the characteristic properties of aldehydes. This, however, is not the case for ketones, which are more stable in the monomolecular form. On the other hand, many of them tend to condense. Two or more molecules can combine, with elimination of water, to form new, usually unsaturated compounds.

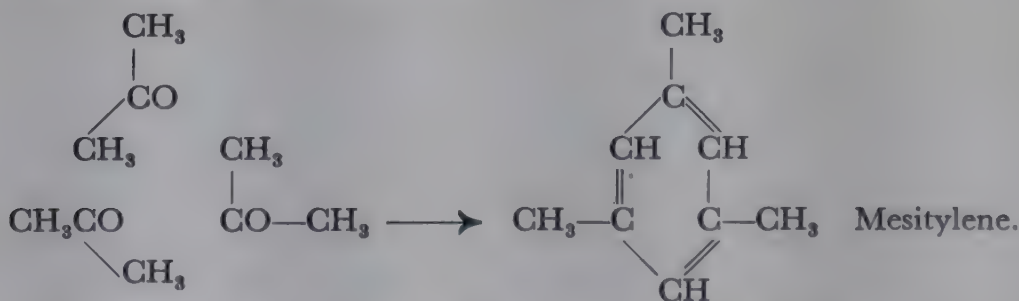
Several such condensations can be brought about with acetone. When treated with strong alkali two molecules combine to give *diacetonyl alcohol* (4-methyl-4-hydroxypentanone-(2)). The process belongs to the aldol condensations:



If acetone is saturated with hydrogen chloride gas and allowed to stand for some time, two unsaturated ketones, *mesityl oxide* and *phorone* are produced. The former is produced from two, the latter from three molecules of acetone:

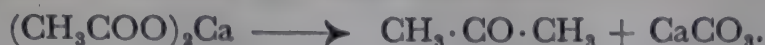


Finally, three molecules of water can be removed from three molecules of acetone by the action of concentrated sulphuric acid. Mesitylene, a hydrocarbon of the benzene series, is thus produced:



Acetone, CH_3COCH_3 . Acetone, the simplest and most important ketone, is found in considerable quantities amongst the products of the dry distillation of wood. It is, however, difficult to isolate the compound in a state of purity from the distillate, so that the process has no great industrial importance. Good yields of acetone can also be obtained by passing acetic acid vapour over heated barium carbonate or pumice-stone. Technically, however, it is prepared by the dry distillation of calcium acetate, which is itself prepared from synthetic acetic acid

or from the acetic acid present in considerable amounts in the distillate from the destructive distillation of wood (pyroligneous acid):



It is further obtained by dehydrogenation of isopropyl alcohol with pieces of brass as catalyst. Processes are also known by which acetone can be obtained from carbohydrates (starch, dextrin, maltose) by bacterial decomposition. The *Bacterium acetoethylicum* produces 10–30 per cent of alcohol, and 6–10 per cent of acetone from starch. Moreover, *Bacillus macerans* gives good yields of acetone from starch.

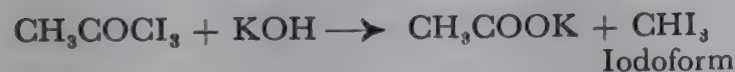
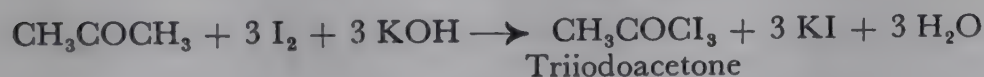
According to a patent of the I. G. Farbenindustrie, acetone can be obtained in good yield by passing acetylene and water vapour over zinc oxide heated to 400°



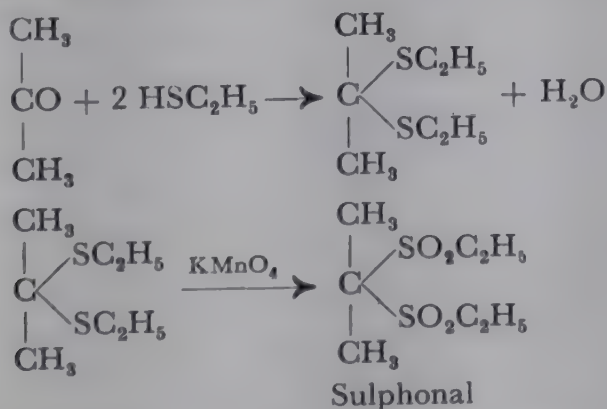
In the urine of diabetic patients (Diabetes mellitus) acetone is often present in considerable quantities. It is formed from acetoacetic acid, $\text{CH}_3\text{COCH}_2\text{COOH}$, a normal product of metabolism, by elimination of carbon dioxide.

Acetone is a clear liquid, with an aromatic smell, miscible with water in all proportions. It is inflammable. It is a very valuable starting material for the syntheses of important products.

Thus chloroform and iodoform can be obtained from acetone, by acting on it with chlorine or iodine, respectively, and alkali. Trichloro- or triiodoacetone is first formed, and this is then readily hydrolysed by the alkali to chloroform or iodoform, and acetic acid:

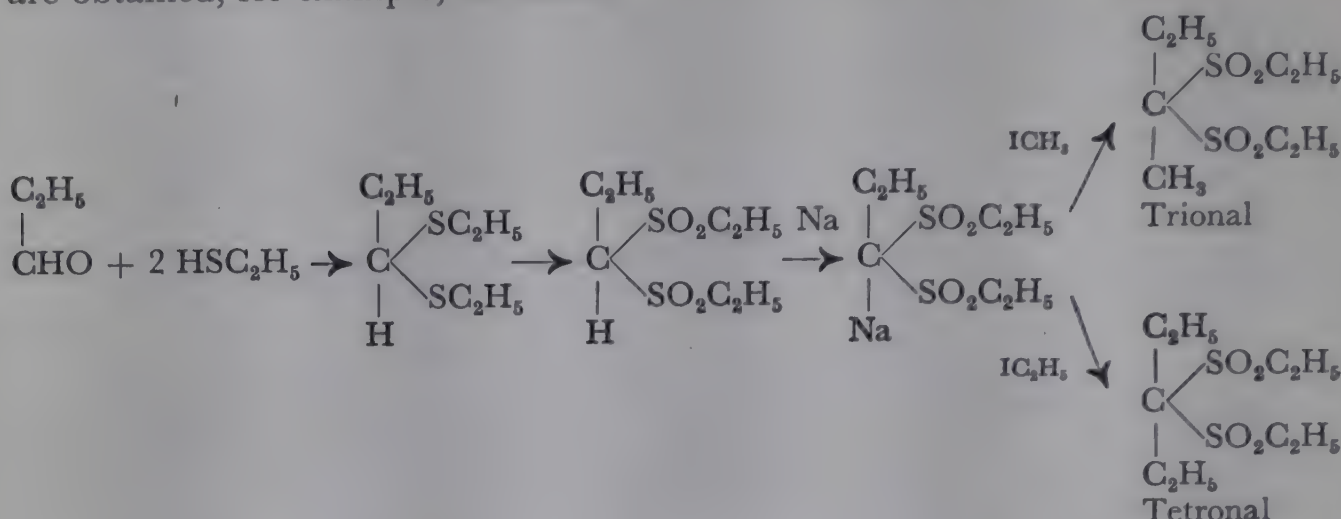


Acetone is also the starting material for the synthesis of the hypnotic *sulphonal*. This is obtained by condensing acetone with ethyl mercaptan, and oxidizing the mercaptol produced by potassium permanganate, giving 2:2-bis-(ethylsulphonyl)-propane, *sulphonal*:



The more detailed investigation of the sulphonal derivatives has shown that the presence of the ethyl groups is necessary for their narcotic action. Homologues

of sulphonal have therefore been prepared, such as *trional*, which contains three ethyl groups, and *tetronal*, which contains four. The narcotic effect is indeed increased by the presence of the larger number of ethyl groups. Trional and tetronal are obtained, for example, as follows:



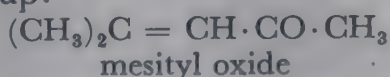
Exceedingly large quantities of acetone are used in the manufacture of smokeless powder for the gelatinization of nitrocellulose. It is also used as a solvent in the manufacture of artificial silk, as a swelling agent in the preparation of plastics (celluloid industry), and as a solvent for acetylene. For a time, acetone was used in the manufacture of an artificial rubber, the so-called acetone caoutchouc, dimethylbutadiene (see p. 61) being formed as an intermediate product.

Acetone-chloroform (chloretone), $(\text{CH}_3)_2\text{C} \begin{array}{l} \text{OH} \\ \diagdown \\ \text{CCl}_3 \end{array}$, is used as an hypnotic and

anæsthetic. Finally, acetone is used in the synthesis of artificial violet perfumes, the ionones (Ch. 54).

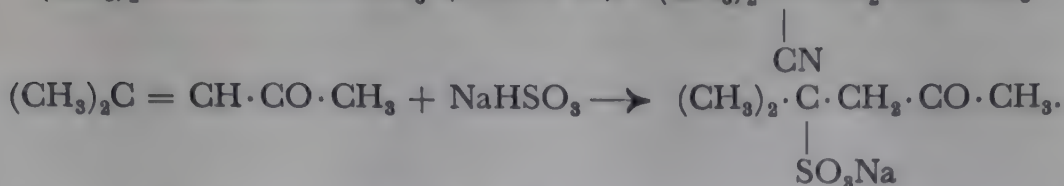
Amongst the numerous **higher ketones** known, three, METHYL HEPTYL KETONE, $\text{CH}_3\text{COC}_7\text{H}_{15}$, METHYL OCTYL KETONE, $\text{CH}_3\text{COC}_8\text{H}_{17}$, and METHYL NONYL KETONE, $\text{CH}_3\text{COC}_9\text{H}_{19}$, are found in oil of rue (*Ruta graveolens*). METHYL AMYL KETONE, $\text{CH}_3\text{COC}_5\text{H}_{11}$ and METHYL HEPTYL KETONE, $\text{CH}_3\text{COC}_7\text{H}_{15}$ are found in Roquefort cheese. They are formed in this case by bacterial decomposition of fatty acids (caprylic and capric acids), and for the same reason they are found in rancid fats (see p. 217). METHYL NONYL KETONE, $\text{CH}_3\text{COC}_9\text{H}_{19}$ and METHYL UNDECYL KETONE, $\text{CH}_3\text{COC}_{11}\text{H}_{23}$, have been isolated from rancid coconut fat.

Unsaturated ketones. Two members of this group, MESITYL OXIDE and PHORONE, have already been mentioned (p. 176). They can be prepared from acetone, and both have their double bonds in the α, β -position with respect to the CO-group:

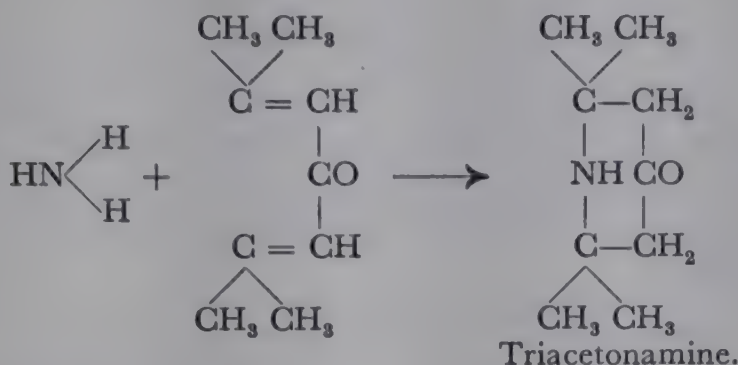


Under the influence of the neighbouring carbonyl group, the $\text{C}=\text{C}$ double bond of these unsaturated ketones becomes very reactive. Numerous reagents, such as ammonia, hydrocyanic acid, and sodium bisulphite, which are ordinarily without effect on the ethylenic linkage, can add on to the double bond in the $\Delta^{\alpha, \beta}$ -ketones:¹

¹ The double bond in unsaturated substances is represented by Δ .

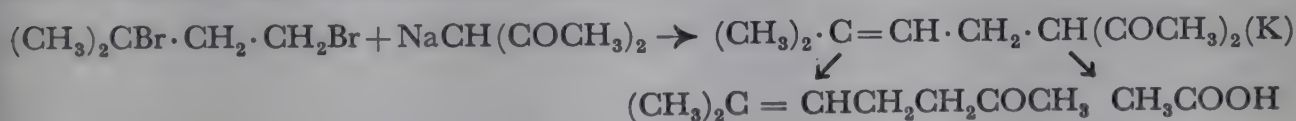


The addition of ammonia across the double bond in phorone leads to a product which is also of interest from the practical point of view. On warming, a heterocyclic substance, "*triacetoneamine*", is produced, which is the starting material for the preparation of some medicinal products:

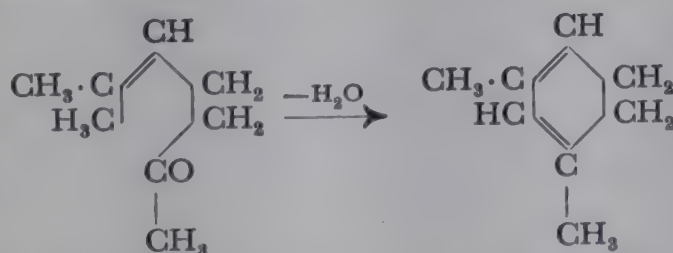


2-METHYL-HEPTEN-(2)-ONE-(6), $(\text{CH}_3)_2\text{C} = \text{CH} \cdot \text{CH}_2\text{CH}_2\text{COCH}_3$, an unsaturated ketone already mentioned on p. 171, is connected in many ways with the aliphatic and cyclic terpenes. Barbier and Bouveault found this compound in various essential oils (e.g. lemongrass oil, linaloe oil, lemon oil, and palmarosa oil), where it occurs, however, only in small quantities. A convenient method of preparing it consists in hydrolysing citral with alkalis, a process which has been described on p. 171.

The structure of this unsaturated ketone can be arrived at not only from its further degradation, but also from total synthesis. Thus Barbier and Bouveault condensed 2-methyl-2:4-dibromobutane with sodio-acetylacetone to give the unsaturated ketone (K), which broke down into acetic acid and methylheptenone when treated with concentrated alkali:

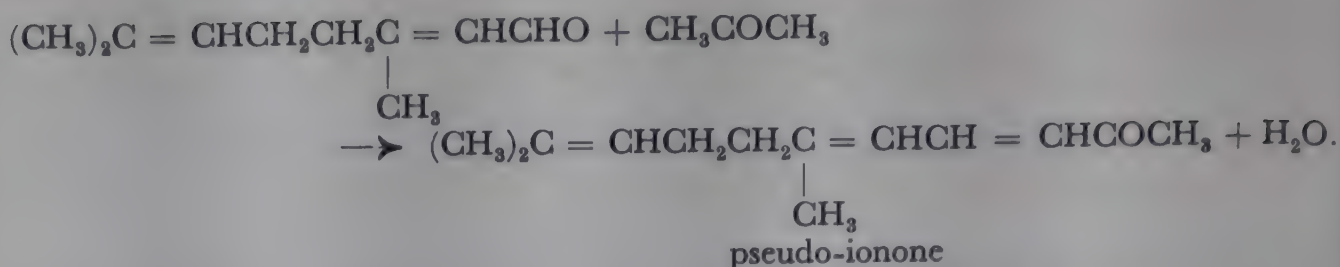


Methylheptenone is a liquid with a flower-like smell, which boils at 170–171°. When treated with moderately concentrated sulphuric acid it loses water and is converted into dihydro-*m*-xylene:



It is the starting point for the preparation of geranic acid (p. 171) from which a large number of syntheses of aliphatic terpenes and camphors (e.g. geraniol, nerol, citral, linalool, etc.) originate.

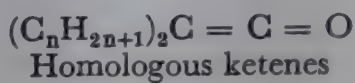
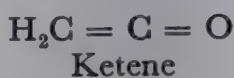
PSEUDO-IONONE is an unsaturated ketone with three double bonds, which is formed by the condensation of citral and acetone in the presence of alkali:



It is used in the preparation of the two ionones, which are artificial violet perfumes. (Ch. 54).

Ketenes¹

The *ketenes*, a class of substances discovered by N. T. M. Wilsmore and by H. Staudinger, contain, like the ketones, a $>\text{CO}$ group. This is linked to another carbon atom by a *double* bond. The simplest ketene is therefore carbonylmethylene, and there are homologues of it in which the hydrogen atoms are substituted by alkyl (or aryl) groups:



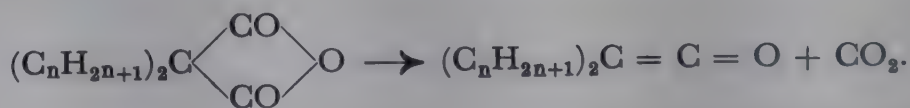
Most ketenes can be prepared from α -halogen-substituted acid halides by removal of the halogen with zinc. Owing to the readiness with which the ketenes react with oxygen it is necessary to carry out their preparation in the absence of air.

Thus, dimethylketene is prepared by the action of zinc on α -bromodimethylacetyl bromide: $(\text{CH}_3)_2\text{CBrCOBr} + \text{Zn} \rightarrow \text{ZnBr}_2 + (\text{CH}_3)_2\text{C} = \text{C} = \text{O}$.

Schmidlin found that the simplest ketene could be obtained by the simple pyrolysis of acetone, which is decomposed into methane and ketene on passing its vapour through a tube containing broken tiles heated to dull redness:

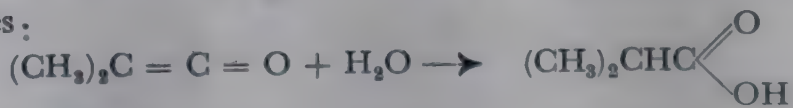


On a technical scale, ketene is generally produced to-day by cracking acetic acid at 600–700°. Ketenes are also readily prepared by the action of heat on the anhydrides of substituted malonic acids:

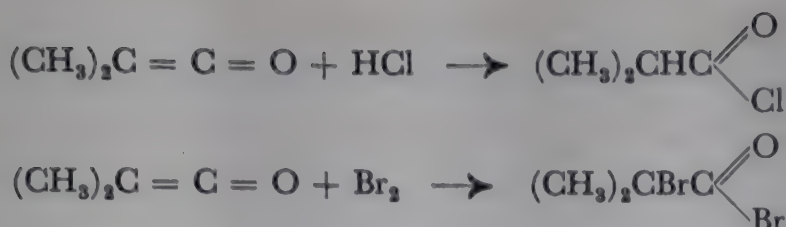


The ketenes belong to the most reactive substances. Their unsaturated nature is due to the system of cumulative double bonds ($>\text{C} = \text{C} = \text{O}$) present in their molecules. According to the nature of the compound which is acting on the ketene, it may add on to one or the other double bond.

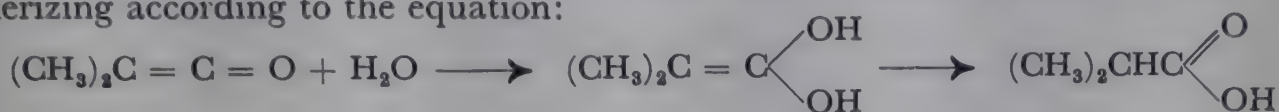
Water converts the ketenes into *acids*, ammonia converts them into acid amides, hydrogen chloride into acid chlorides, and halogens into the α -halogen-substituted acid halides:



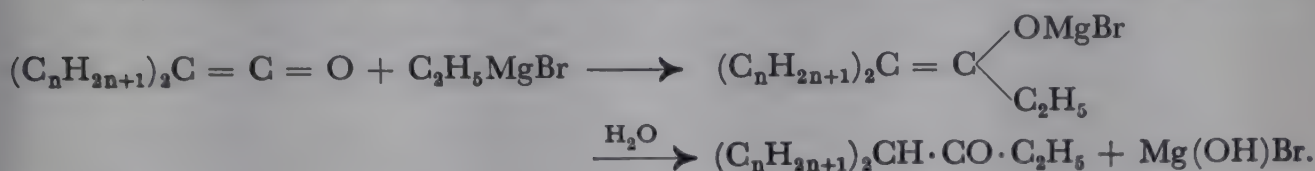
¹ See H. STAUDINGER, *Die Ketene*, Stuttgart, (1912).



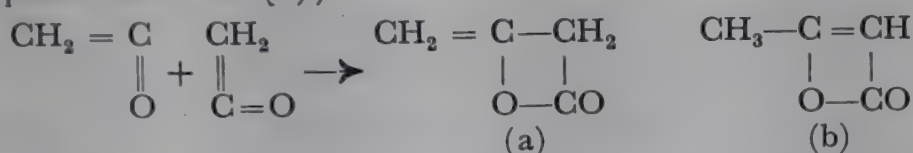
This addition of water, ammonia, etc., may possibly take place, not by direct addition across the $\text{C}=\text{C}$ double bond in the ketene, but initially by addition across the $\text{C}=\text{O}$ bond, the unstable intermediate products then isomerizing according to the equation:



Alkylmagnesium salts also add on across the carbonyl bond of the ketenes:

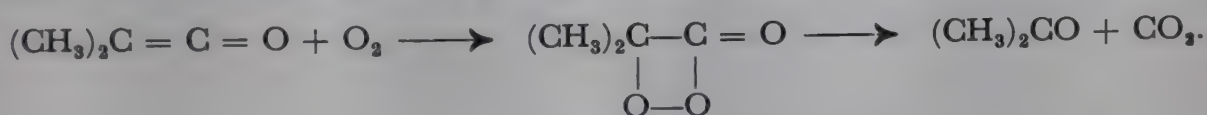


The tendency towards polymerization is characteristic of the ketenes. Dimeric products are thus formed which probably have the formula (a) (in the vapour possibly in equilibrium with (b)):



These easily depolymerize on heating giving the simple ketenes.

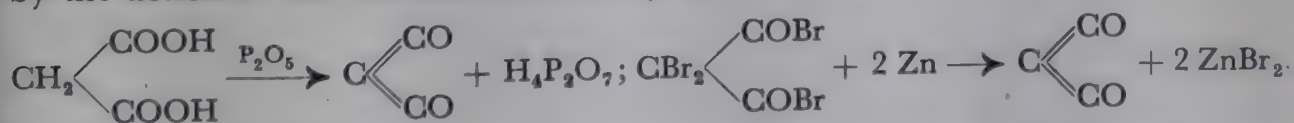
The ease with which the ketenes react with oxygen has already been mentioned. They are autoxidizable, and form, at low temperatures, very unstable, explosive peroxides with oxygen. On careful warming, these decompose into ketones and carbon dioxide. The reaction is formulated as follows (Staudinger):



In addition, more stable simple ketene oxides, $[(\text{C}_n\text{H}_{2n+1})_2\text{C}-\text{CO}]_x$, are known,

which are formed by the action of oxygen on ether solutions of ketenes at ordinary temperatures.

The lowest oxide of carbon, *carbon suboxide*¹, $\text{O}=\text{C}=\text{C}=\text{C}=\text{O}$, discovered by Diels, may be included in the group of ketenes. It is formed by heating malonic acid and phosphorus pentoxide to 140–150° in a vacuum, or by the action of zinc on dibromomalonyl dibromide:



It possesses a very unpleasant smell, reminiscent of acrolein, and irritates powerfully the eyes and lungs. It is poisonous, and burns with a sooty blue flame. Its boiling point is 7°.

¹ See E. DONATH and O. BURIAN, *Kohlensuboxyde*, Stuttgart, (1924).

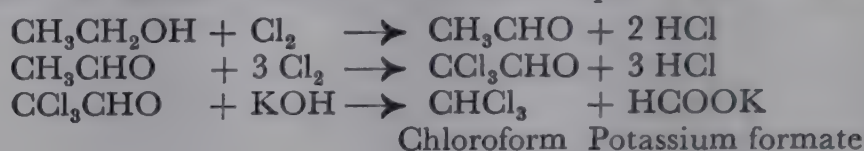
Section III. Compounds with a trivalent function

CHAPTER 10

THE TRIVALENT HALOGEN FUNCTION

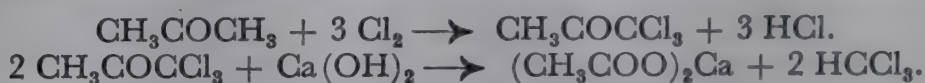
The tri-halogen derivatives of methane, HCX_3 , are the simplest and most important halogen compounds in which three halogen atoms are linked to the same carbon atom. They are used in medicine under the names *chloroform*, CHCl_3 , *bromoform*, CHBr_3 , and *iodoform*, CHI_3 .

CHLOROFORM. This compound is obtained from alcohol or acetone, and in more recent times, from carbon tetrachloride. If ethyl alcohol is treated with chlorine and alkali, or bleaching powder, it is first oxidized to acetaldehyde. This reacts with more chlorine and is converted into trichloroacetaldehyde, or chloral, CCl_3CHO . Chloral is unstable in alkaline solution and decomposes into formic acid and chloroform:



Chloroform was discovered in this way in 1831 by Liebig and by Soubeiran.

Similarly, chloroform can be obtained from acetone and bleaching powder:



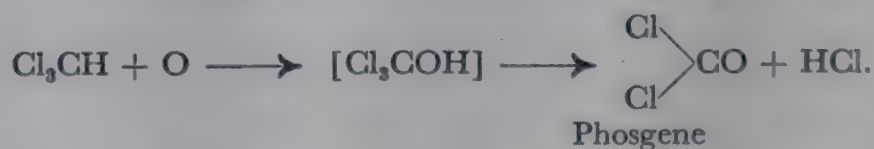
All compounds containing the group CH_3COC — or $\text{CH}_3\text{CH}(\text{OH})$ — give chloroform when treated with chlorine and alkali.

After carbon tetrachloride had become an easily accessible substance, a method of obtaining chloroform from it by partially reducing it with zinc and sulphuric acid has been worked out: ✓



This method of preparing chloroform has, however, at present hardly any technical importance.

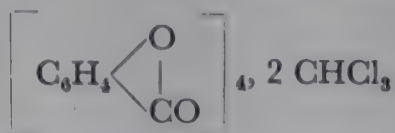
Chloroform is a heavy, colourless, liquid with a sweetish smell. It boils at 61° , and does not burn. It dissolves only to a slight extent in water, but is readily soluble in alcohol and ether. It is gradually oxidized in damp air, *phosgene*, a poisonous gas which strongly attacks the respiratory organs, being produced:



Bad after-effects, and lesions accompanying the use of chloroform as an anæsthetic can be traced to the presence of phosgene and similar decomposition products. In order to avoid the effect of phosgene, 1 per cent of alcohol is added to the chloroform used for medicinal purposes. This destroys phosgene by combining with it to form the neutral ethyl carbonate:



Perfectly pure chloroform can be obtained by freezing the impure product (m.p. -63°). In another method it is combined with an anhydride of salicylic acid (tetrasalicylide), when a double compound is formed which crystallizes well:

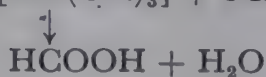


On warming, pure chloroform distils off.

Alkalis easily remove the chlorine atoms from chloroform. If sodium ethylate is used, ethyl orthoformate is produced:



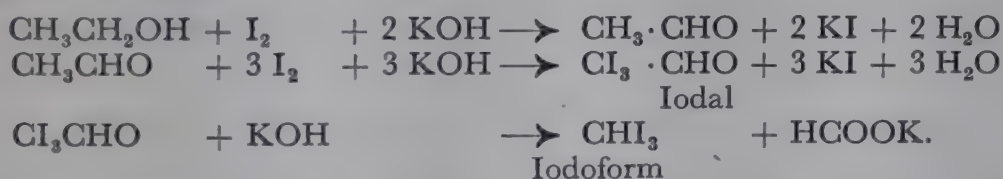
With aqueous alkalis the usual "meta" form is obtained instead of the unstable orthoformic acid: $\text{CHCl}_3 + 3 \text{KOH} \longrightarrow [\text{HC(OH)}_3] + 3 \text{KCl.}$



Chloroform is used extensively as an anæsthetic. It is also used in industry as a solvent and extracting agent, particularly for resins and oils.

BROMOFORM, CHBr_3 . This compound is prepared in a similar way to chloroform. Calcium hypobromite, or bromine and alkali are allowed to act upon alcohol or acetone. Bromoform is a colourless liquid with a smell similar to that of chloroform. It boils at 148° . It is used in medicine in the treatment of whooping-cough, and for that purpose is mixed with 4 per cent of alcohol to prevent decomposition. It is also used in sedimentation methods for the separation of sands, owing to its high specific gravity.

IODOFORM, CHI_3 . Iodoform is produced when iodine and alkali act upon ethyl alcohol or acetone:



Technically, iodoform is prepared by electrolysing a dilute alcoholic or acetone solution of potassium iodide to which some sodium carbonate has been added. At the cathode caustic potash is formed from the liberated potassium and water, and at the anode iodine is set free. These two substances then react with the alcohol or acetone in the manner indicated by the above equations, and iodoform separates.

Iodoform is a yellow solid, with a strong, characteristic smell. It melts at 120° . The substance is slowly decomposed on exposure to light and air. In its chemical reactions it behaves like chloroform.

Iodoform is largely used in medicine as an antiseptic. It prevents the festering of wounds. The bactericidal action, however, is due only slightly or not at all to the direct action of iodoform itself. But when it comes into contact with the organic matter iodine is slowly liberated, and it is this that acts as the antiseptic. Some people are hypersensitive towards iodoform, and become affected with eczema when they are treated with it. In order to avoid the unpleasant smell of iodoform it is often combined with other substances (proteins, hexamethylene-

tetramine), or other iodine preparations (iodole, aristole, etc.) are substituted for it. The importance of iodoform, however, has been scarcely affected by them.

FLUOROFORM, CHF_3 (b.p. -82°), can be obtained, for example, from bromoform by heating it with antimony fluoride. It is not very active either chemically or physiologically.

CHAPTER 11.

TRIVALENT NITROGEN FUNCTIONS.

HYDROCYANIC ACID. NITRILES

Hydrocyanic acid, or Prussic acid, HCN

Hydrocyanic acid and its compounds are not infrequently found in the vegetable kingdom as normal products of metabolism. In the free state it is contained, for example, in the seeds of the Java tree, *Pangium edule*, in *Manihot utilissima* and *aïpi*, and in *Dimorphotheca spectabilis*. Cyanogenetic glucosides occur widely in fruits, e.g. almonds, cherry, peach, apricot, and apple kernels. Compounds of hydrocyanic acid are therefore also found in cherry brandy, and other fruit spirits. They have moreover been detected in *Phaseolus lunatus* (Rangoon beans). The best known cyanogenetic glucoside is *amygdalin*, which is present in bitter almonds. It decomposes on treatment with acids, or with the enzyme “*emulsin*” present in the almonds, into one molecule of benzaldehyde, one molecule of hydrocyanic acid, and two molecules of glucose, and possesses the constitution:



In the laboratory, hydrocyanic acid is usually prepared from one of its complex salts, *potassium ferrocyanide* (or “*yellow prussiate of potash*”) $\text{K}_4[\text{Fe}(\text{CN})_6]$ by acting on it with sulphuric acid:



The hydrogen cyanide is readily volatile, and is condensed in a strongly-cooled receiving vessel.

Technically, hydrocyanic acid can be made by the decomposition of trimethylamine which is passed through red-hot chamotte retorts. The trimethylamine breaks down at $800\text{--}1000^\circ$ into hydrocyanic acid and methane:



The molasses from beet-sugar is the starting material. They contain about 4 per cent of nitrogen in the form of betaine (see p. 296). On heating, the betaine gives trimethylamine. The vapour is passed through the heated retorts, and a gaseous mixture containing up to 7 per cent of hydrogen cyanide is obtained.

In earlier times cyanides were often prepared from nitrogenous organic substances, such as blood, by heating them with potash, or an alkali metal, and iron filings. The carbon and nitrogen of the organic substances thus combined with the alkali to give alkali cyanides, which further combined with the iron to give ferrocyanides, e.g. potassium ferrocyanide, $\text{K}_4[\text{Fe}(\text{CN})_6]$:

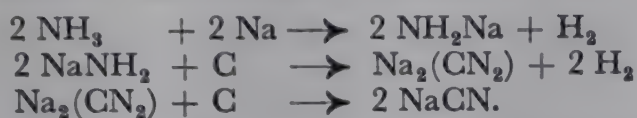


The simple alkali cyanides can be obtained from potassium ferrocyanide by fusion with potash, or better sodium:



Cyanogen compounds are also obtained as by-products of the distillation of anthracite. The cyanogen content of the unpurified gas is considerable. The cyanogen is absorbed in the iron oxide purifiers, forming chiefly $\text{Fe}(\text{CN})_2$, which is then worked up into sodium ferrocyanide.

Besides the preparation of hydrocyanic acid from beet-sugar molasses wash, a recent technical process of great importance is the synthesis of sodium cyanide from ammonia, metallic sodium, and coke (Deutsche Gold- und Silberscheideanstalt). Ammonia and sodium give, at about 600° , sodamide, which, with the carbon, gives sodium cyanamide. On heating to a still higher temperature (800°) this combines with carbon to give sodium cyanide:



These two processes supply the major portion of the alkali cyanides used in the extraction of gold and silver from their ores.

The direct synthesis of hydrogen cyanide from its elements is of theoretical interest. This is carried out by passing hydrogen and nitrogen through an arc struck between carbon poles. The reaction temperature must, however, be very high, lying above 1800° .

Anhydrous hydrocyanic acid is a colourless liquid. It boils at 26° , and freezes on cooling (m.p. -15°) to thread-like crystals. It is inflammable, and is soluble in water and alcohol in all proportions. It has a very high dielectric constant (about 95). The compound is an exceedingly powerful poison, very small quantities being fatal. The toxic action of hydrocyanic acid depends upon the fact that it stops oxidation processes in the cells. Its smell is characteristic, and recalls that of bitter almonds.

Pure hydrocyanic acid can be kept for fairly long periods. Aqueous solutions decompose more quickly. A brown precipitate containing a large percentage of nitrogen, is produced.

Hydrocyanic acid finds many uses in synthetic chemistry. It was also proposed as a disinfecting agent for rooms, and for the prevention of damage to fruit-trees by pests. Its use for these purposes, on account of its poisonous nature, must be undertaken only with the greatest care.

So far we have formulated hydrocyanic acid as $\text{H}-\text{C}\equiv\text{N}$. However, a tautomeric form of the compound, $\text{H}-\text{N}=\text{C}$, also comes into consideration. In fact, there are organic derivatives of hydrogen cyanide derived from the first form, and others from the second. They are called the *nitriles* and the *isonitriles* respectively. Hydrogen cyanide itself is known in only one form. Probably it is an allotropic mixture of the two isomeric forms (I) and (II):

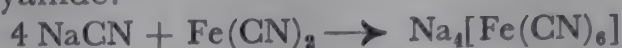


The alkali, alkaline-earth, and mercury cyanides are soluble in water and are very poisonous. Solutions of the alkali cyanides react alkaline owing to partial hydrolysis:

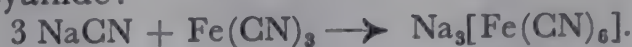


The cyanides of the other metals dissolve with difficulty or not at all in water.

Use is made of the almost insoluble silver cyanide in the quantitative estimation of silver or cyanide ions. These metal cyanides, however, often have the property of dissolving readily in solutions of the alkali cyanides. This depends upon the fact that they combine with the cyanides of the alkali metals to give so-called "complex salts". Thus four molecules of sodium cyanide combine with one of ferrous cyanide to give sodium ferrocyanide:



or three molecules of sodium cyanide combine with one of ferric cyanide, $\text{Fe}(\text{CN})_3$, to give sodium ferricyanide:



These complex cyanides, also known as "*cyno-salts*", dissociate in aqueous solution into positive alkali-metal ions and negative complex ions $[\text{Fe}(\text{CN})_6]^{4-}$ and $[\text{Fe}(\text{CN})_6]^{3-}$. They do not give cyanide ions. This is in agreement with the fact that, compared with the alkali cyanides, they are relatively weak poisons.

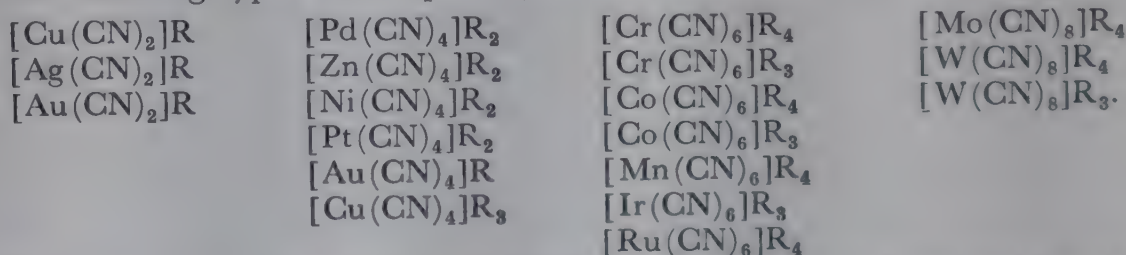
Sodium ferrocyanide and sodium ferricyanide are the sodium salts of two complex acids, *ferrocyanic acid*, $\text{H}_4[\text{Fe}(\text{CN})_6]$, and *ferricyanic acid*, $\text{H}_3[\text{Fe}(\text{CN})_6]$, which can be obtained from them in crystalline form by the addition of mineral acids:



These complex cyanides belong to the class of coordination compounds (A. Werner). The cyanide radicals are symmetrically grouped in space about a central atom, the coordination centre, (in our case, iron), and form with it the "inner sphere" or complex. This is so stable that it is not broken down by water. It represents a negative ion, of which the valency depends upon that of the central atom, being given by six minus the valency of the central atom.

The maximum number of cyanide radicals that can be grouped round the central atom depends on the chemical nature of the latter. For most elements it is 6, but for some it is 2, 4, or 8. The maximum number of monovalent groups that can be attached to the central atom is called the *coordination number*. Its magnitude is determined by the spatial arrangement of the groups. If there are six groups, they occupy the apices of an octahedron, with the central atom in the middle. Four groups can be arranged either in a plane or tetrahedron, etc.

The following types of complex cyanides are known, e.g.:



The large number of such complex salts is still further increased by the fact that individual cyanide groups can be replaced by other groups (H_2O , NH_3 , NO , etc.). Of the very numerous compounds of this type, *sodium nitroprusside*, $[\text{Fe}(\text{CN})_5\text{NO}]\text{Na}_2 \cdot 2 \text{H}_2\text{O}$, may be mentioned. It is a red, crystalline substance, which is used in analysis for the detection of the sulphide ion (hydrogen sulphide and its salts), with which it gives an intense violet coloration.

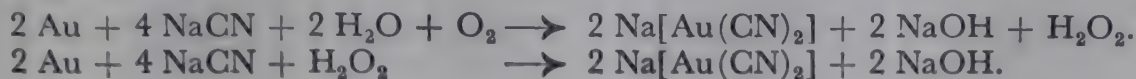
Ferric ferrocyanide, or Prussian Blue, is also important in analysis. It is obtained as an intense blue precipitate on adding potassium ferrocyanide to a

ferric salt, and its formation is used as a qualitative test for ferric ions, and for the colorimetric determination of ferric iron:



Paper coated with barium platinocyanide $\text{Ba}[\text{Pt}(\text{CN})_4]$ is used as a screen for detecting X-rays and other short-wave radiations, which are converted by the salt into radiations of longer wave-length, and thus made visible to the eye.

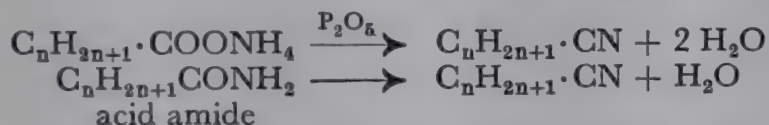
Sodium cyanide is the most important cyanide, since its solution is used in the extraction of gold from its ores (cyanide process). The solution readily dissolves gold in the presence of air. The reactions which take place are represented by the following equations:



Nitriles, $\text{C}_n\text{H}_{2n+1}\cdot\text{C}\equiv\text{N}$

Nitriles, or alkyl cyanides, are the esters of hydrocyanic acid. They can be synthesized, more or less smoothly, in many ways. In addition to the names "methyl cyanide", "ethyl cyanide", etc., others, derived from the names of the acids with the same number of carbon atoms are often used, e.g. acetonitrile, etc.

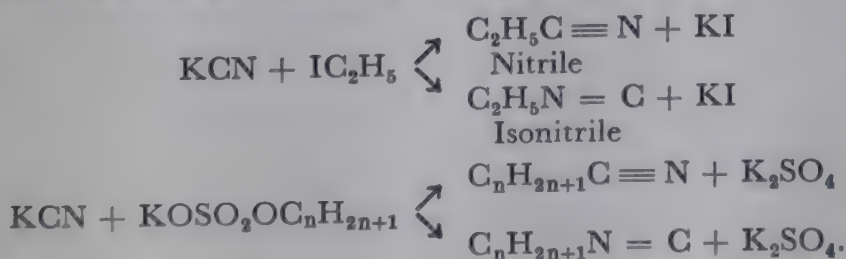
PREPARATION OF NITRILES. (a) Carboxylic acids can be converted into nitriles if their ammonium salts, or better their amides, are distilled with a dehydrating agent, usually phosphorus pentoxide. Phosphorus pentachloride or thionyl chloride is also suitable for the dehydration of acid amides (Dumas):



These methods of preparation also provide a proof that the alkyl radical is linked to carbon and not to nitrogen in the nitriles, since this is true of the carboxylic acids and amides from which they are synthesized.

A newer method of synthesizing nitriles is to pass the vapour of the carboxylic acid or its ester, mixed with ammonia, over heated alumina at 500° .

(b) Another method of obtaining alkyl cyanides is to alkylate the cyanide salts (Williamson, Pelouze). Nitriles are thus obtained in good yield by heating potassium cyanide with alkyl halides in dilute alcoholic solution, or by distilling with alkyl hydrogen sulphates. However, the unpleasant-smelling isomeric *isonitriles* or *carbylamines* are obtained in small quantities as by-products. This is another case of a phenomenon already met with (nitro-compounds) where alkylation of salts derived from a tautomeric acid gives rise to a mixture of alkyl compounds:



¹ According to Reihlen the compounds of ferrocyanic acid and similar complex cyanogen acids with heavy metals are not salts of these acids, but are complex multinuclear compounds, e.g. Prussian Blue $[\text{Fe}(\text{CN})_6\text{Fe}]\text{K}$.

The isonitriles can easily be separated from the nitriles by shaking with hydrochloric acid, which hydrolyses them to amines and formic acid.

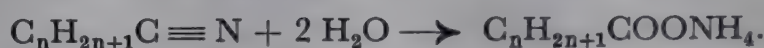
(c) The oximes of the aldehydes lose water when treated with acetic anhydride or thionyl chloride, being converted into nitriles:



PHYSICAL PROPERTIES. The lower members of the series of alkyl cyanides are liquids and have a not unpleasant smell. The higher members are crystalline solids. They are good solvents for some salts. They are much less poisonous than hydrocyanic acid.

	b.p.	m.p.		b.p.	m.p.
CH_3CN	81.5°	— 44°	$n\text{-C}_6\text{H}_{13}\text{CN}$	183°	
$\text{C}_2\text{H}_5\text{CN}$	98°	—103°	$n\text{-C}_7\text{H}_{15}\text{CN}$	199°	
$n\text{-C}_3\text{H}_7\text{CN}$	116°		$n\text{-C}_8\text{H}_{17}\text{CN}$	215°	
$n\text{-C}_4\text{H}_9\text{CN}$	141°				
$n\text{-C}_5\text{H}_{11}\text{CN}$	162°		$\text{C}_{15}\text{H}_{31}\text{CN}$	b.p. 193°	31°
			$\text{C}_{17}\text{H}_{35}\text{CN}$	b.p. 214°	41°

CHEMICAL PROPERTIES. (a) On treatment with acids or alkalis the nitriles are easily converted into carboxylic acids by hydrolysis:

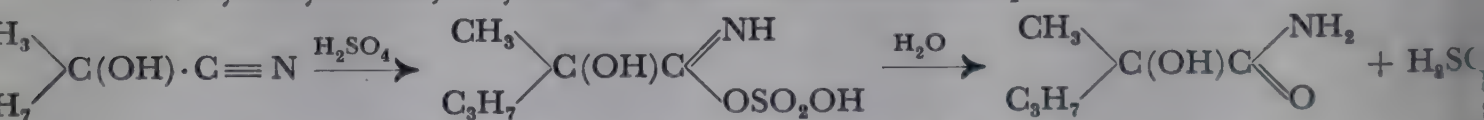


It is possible by suitably choosing the reaction conditions to stop the reaction when only one molecule of water has been added, the acid amides being produced. This is, for example, often the case when the hydrolysis is carried out with 96 per cent sulphuric acid, or hydrogen peroxide:



These reactions are thus the reverse of those used in the synthesis of the nitriles, where water is eliminated from amides or ammonium salts of the carboxylic acids.

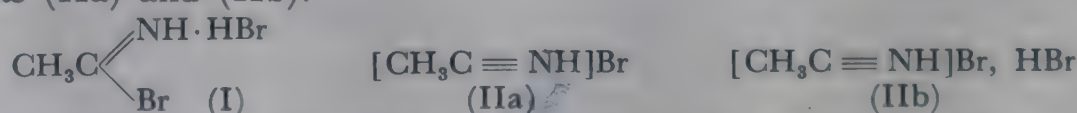
It appears that the hydrolysis of nitriles by sulphuric acid takes place through the formation of addition products of an "imide-sulphuric acid" type. In the hydrolysis of the α -hydroxy-nitriles, they can be isolated as intermediate products:



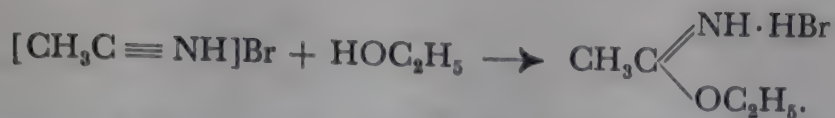
(b) By reduction of nitriles with sodium and alcohol primary amines are formed (Mendius): $\text{C}_n\text{H}_{2n+1}\text{CN} + 2\text{H}_2 \longrightarrow \text{C}_n\text{H}_{2n+1}\cdot\text{CH}_2\text{NH}_2$.

The conversion of alkyl cyanides into secondary amines by catalytically activated hydrogen has already been mentioned in connection with the latter compounds.

(c) Dry hydrogen halides add on to nitriles. Very reactive substances, the "imino-halides", are produced. These were formerly regarded as having the formula (I), but are now considered to be nitrilium halides, corresponding to the formulæ (IIa) and (IIb).



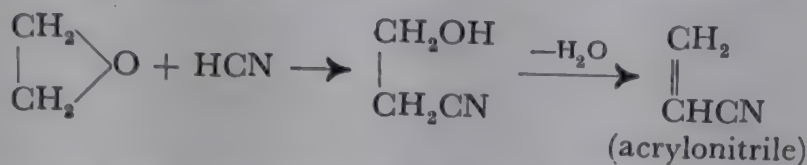
They have sometimes been used for syntheses, and are, for example, converted by alcohols into the imino-ethers:



(d) By the action of alkylmagnesium salts on nitriles, ketones are produced (see p. 173).

(e) When treated with sodium or sodium ethylate, nitriles polymerize to di- or trimolecular products. The latter, the so-called *cyanoalkines*, are heterocyclic compounds and will be considered again elsewhere (see pyrimidines). Certain nitriles of the formula RCH_2CN (e.g. phenylacetonitrile) give crystalline sodium salts when treated with sodium in an inert atmosphere e.g. $[\text{C}_6\text{H}_5\text{CHCN}]\text{Na}$ (see also Ch. 58).

Among the nitriles with an unsaturated hydrocarbon group we must mention acrylonitrile, which is, for example, produced from ethylene oxide in the following way:



It readily polymerizes and therefore serves for the manufacture of artificial materials and synthetic rubber (Buna N).

Isonitriles, $\text{C}_n\text{H}_{2n+1}\text{N} = \text{C}$. The isonitriles or carbylamines are isomeric with the nitriles and are derived from the second form of hydrocyanic acid, HNC . Their formation from a primary amine, chloroform, and alkali (A. W. Hofmann), which has already been mentioned in connection with the amines, proves their constitution:



Since the alkyl radical in the amine is directly linked to nitrogen, it may be concluded that this will also be the case in the isonitriles.

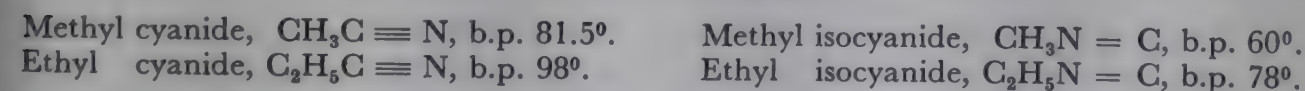
Isonitriles are also formed in good yield by the action of an alkyl halide on silver cyanide (Gautier):



and, as already mentioned, in small amounts, together with the nitriles, by the alkylation of potassium cyanide.

Recently the isonitriles have been formulated with a semipolar bond: $\bar{\text{C}}\equiv\text{NR}^+$. This is in agreement with the octet theory, and with the experimental values of the parachors of the isonitriles.

The isonitriles are distinguished from the nitriles by their repulsive smell, their greater toxicity, and their lower boiling point:



The two classes of substances show, of course, great differences in chemical behaviour. Thus, the isonitriles are easily decomposed by aqueous acids to amines and formic acid:



On the other hand they are not affected by alkalis. Addition of hydrogen gives secondary amines: $\text{C}_n\text{H}_{2n+1}\text{N} = \text{C} + 2 \text{H}_2 \rightarrow \text{C}_n\text{H}_{2n+1}\text{NHCH}_3$.

On heating they undergo rearrangement, forming nitriles:

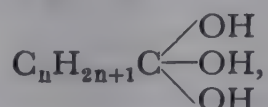


CHAPTER 12

THE TRIVALENT OXYGEN FUNCTION. MONOBASIC CARBOXYLIC ACIDS

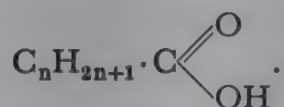
Saturated monobasic carboxylic acids. Fatty acids.

If the three hydrogen atoms at the end of a hydrocarbon chain are considered to be replaced by three hydroxyl groups:



the formula of a compound is obtained which does not exist in the free state, but of which derivatives, particularly esters, are known. Such a substance is called an *orthocarboxylic acid*. It represents the trivalent hydroxyl function.

In all attempts to obtain free orthocarboxylic acids, one molecule of water is eliminated. The reaction products are the so-called meta-forms of the carboxylic acids, commonly called *carboxylic acids*. Their constitution is given by:



It is these carboxylic acids that are now to be considered. The derivatives of the ortho-acids are of less importance. They will be briefly mentioned later (p. 220).

The group $\text{---C} \begin{array}{l} \diagup \text{O} \\ \text{---} \\ \diagdown \text{OH} \end{array}$ has been called the "*carboxyl*" group, the suggestion

being due to Baeyer. The carboxylic acids can thus be called the carboxyl derivatives of the hydrocarbons. They can also be regarded as derivatives of water, in which a hydrogen atom of the water has been replaced by the radical $\text{C}_n\text{H}_{2n+1}\text{CO}\text{---}$:

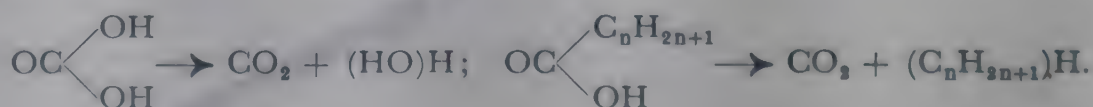


This is not a mere arbitrary comparison, since the group $\text{C}_n\text{H}_{2n+1}\text{CO}\text{---}$ can be transferred unchanged to many other compounds. It is therefore given the special name of *acyl radical* (or acid radical), and the carboxylic acids may be defined as the acyl derivatives of water.

Finally, it is also convenient to regard the carboxylic acids as derivatives of carbonic acid, one of the hydroxyl groups of the latter having been replaced by an alkyl radical:



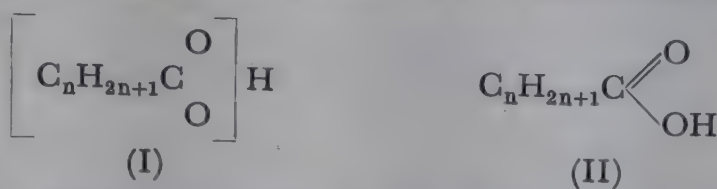
The connection between the two compounds is more than formal in nature, for it is easy to drive off carbon dioxide from both carbonic acid and the carboxylic acids:



It is well-known that acids dissociate in aqueous solution to a more or less considerable extent into hydrogen ions and negative acid ions. The hydrogen atoms in, say, dissociated sulphuric acid, or dissociated carbonic acid, are, therefore, no longer combined with an oxygen atom, but are free. The formulæ of such acids may therefore be conveniently written according to Werner's coordination theory, in the following manner:



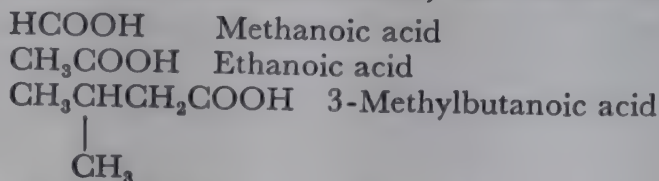
Hantzsch has pointed out that the same is true of carboxylic acids dissolved in water, and that in aqueous solution there is an equilibrium between the ionized form (I), which is also the form of the true, soluble salts, and form (II), which cannot dissociate, and from which the esters and pseudo-salts are derived:



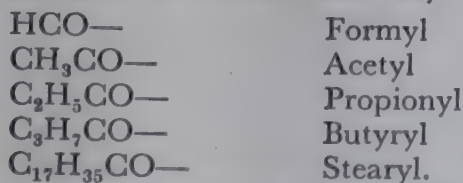
When, in what follows, the formula (II) which has been in use for a long time, is employed, it must be remembered that in reactions occurring in aqueous solution, particularly neutralization reactions, the acids should be formulated with the acid formula (I).

NOMENCLATURE. The aliphatic carboxylic acids are also called fatty acids, since various of the middle and higher members of the series occur in fats, and can be isolated from them. For most of the carboxylic acids, common names are in use (e.g. formic acid, acetic acid, butyric acid, stearic acid, etc.). They can, of course, be named as carboxyl derivatives of the hydrocarbons, such as methane-carboxylic acid, $\text{CH}_3 \cdot \text{COOH}$, ethanecarboxylic acid, $\text{C}_2\text{H}_5\text{COOH}$.

According to the Geneva nomenclature, the names are formed as follows:



The names of the acyl radicals are formed from those of the corresponding acids, the ending -yl being used to denote the acyl nature of the substance:

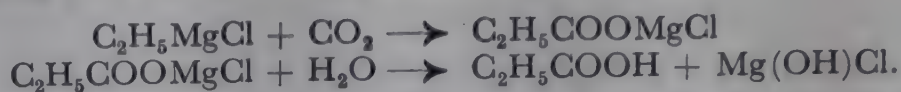


METHODS OF FORMATION. (a) A simple, and theoretically very interesting synthesis of carboxylic acids is the *addition of sodium alkyls to carbon dioxide*. This method, which, however, is limited to the preparation of sodium acetate and propionate, gives an excellent proof of the constitution of the carboxylic acids:



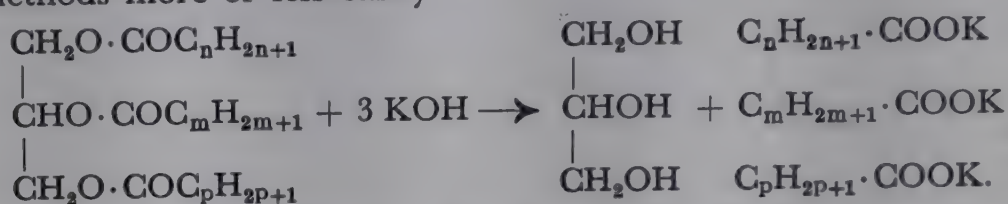
Related to this method is the preparation of fatty acids from alkylmagnesium salts, which is important because of the ease with which the Grignard reagents can

be obtained. Dry carbon dioxide is passed into the ethereal solution of the alkyl-magnesium salt, and the product is acted upon by water:



(b) Fatty acids can also be prepared by the *oxidation of paraffin hydrocarbons*, as stated earlier (p. 32-3). The process is not often used when it is desired to obtain a uniform product.

(c) The latter method, the *hydrolysis of fats and fatty oils*, is one of the most important sources of many carboxylic acids. Fats and fatty oils are esters of the trihydric alcohol glycerol with various fatty acids containing a fairly large number of carbon atoms. If they are treated with superheated steam, or better with alkalis, glycerol and a mixture of fatty acids is obtained, which can be separated by various methods more or less easily:



Whilst the fats are important starting materials for the preparation of the middle and higher members of the series of carboxylic acids, sometimes the "*essential oils*" and *fruit esters* of plants occupy the same position as regards the lower acids. Fruit esters are esters of simple fatty acids with monohydric alcohols. By hydrolysing them the acids are obtained.

A few carboxylic acids are found in plants in the free state, such as formic acid in stinging nettles, fruits, and pine needles, *isovaleric acid* in valerian root, and *isobutyric acid* in the carob bean.

(d) A convenient method of preparing many carboxylic acids is the oxidation of *primary alcohols* (see p. 85-6) and *aldehydes* (see p. 161). Formic acid, acetic acid, propionic acid, and others are made commercially by this method. The oxidation can be brought about by atmospheric oxygen in the presence of catalysts, or with chromic acid, and more seldom with manganese dioxide or nitric acid. In some cases it is also convenient to bring about the oxidation biochemically, with the help of micro-organisms (formation of acetic acid from alcohol with the acetic fungi).

(e) The alkyl halides can be converted into carboxylic acids through the nitriles (see pp. 75 and 188):



The hydrolysis of trihalogen compounds, $\text{C}_n\text{H}_{2n+1}\text{CCl}_3$ into fatty acids is of less interest, since only the first members of that series (chloroform etc.) are easily obtainable:

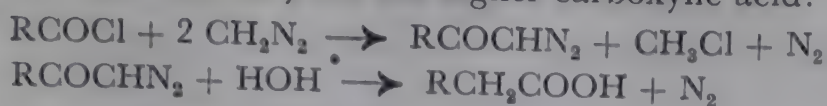


(f) Technically, certain carboxylic acids are made from alcohols and carbon monoxide at high pressures and temperatures of 125-180°, in the presence of boron fluoride and water:

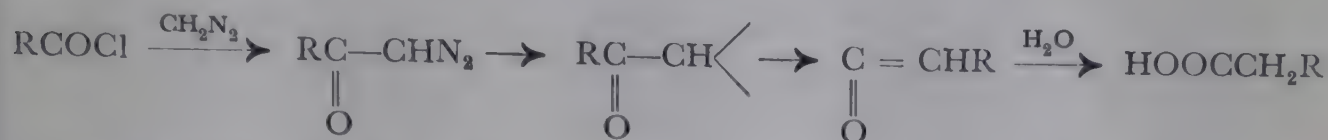


(g) For the preparation of a higher carboxylic acid from its lower homologue

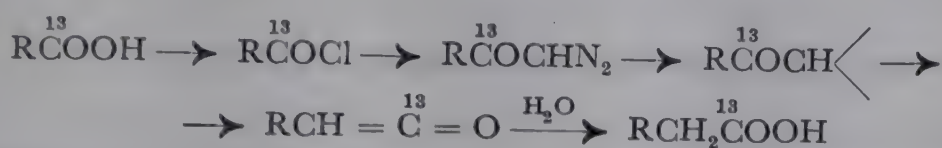
the method of Arndt and Eistert may be used. The method depends on the reaction of an acid chloride with diazomethane to give a diazoketone, which then loses nitrogen and adds on water to yield the higher carboxylic acid:



The course of the reaction involves a rearrangement, and may be expressed by the following formulæ:



The course of the Arndt-Eistert reaction has been proved in the following way: When benzoic acid containing the carbon isotope C^{13} in the carboxyl group is converted into phenylacetic acid, then the carbon C^{13} in the latter compound is again found in the carboxyl group:



PHYSICAL PROPERTIES: The lower fatty acids are mobile liquids, the middle ones are oils, and the higher ones are crystalline solids. The odour of the first members is pungent, whilst the middle ones smell of rancid butter. The highest, are sparingly volatile, and odourless. Only formic, acetic, and propionic acids mix with water in all proportions, and as the series is ascended the solubility in water rapidly decreases, and finally becomes zero.

The melting point increases as the series is ascended, but not regularly. The acids with an even number of carbon atoms melt at higher temperatures than those which immediately follow them, and contain one carbon atom more. The fatty acids therefore fall into two series as regards melting point, one comprising those acids with an even number of carbon atoms, the other those with an odd number (A. v. Baeyer). In both series the difference between the melting points of adjacent members decreases as the series is ascended.

		b.p.	m.p.	Δ	m.p.	Δ
$\text{C}_6\text{H}_{12}\text{O}_2$	Caproic acid	205°			— 1.5°	
$\text{C}_7\text{H}_{14}\text{O}_2$	Oenanthic acid	223°	—10.5°			18.0°
$\text{C}_8\text{H}_{16}\text{O}_2$	Caprylic acid	237°		23.0°	+16.5°	
$\text{C}_9\text{H}_{18}\text{O}_2$	Pelargonic acid	254°	+12.5°			14.9°
$\text{C}_{10}\text{H}_{20}\text{O}_2$	Capric acid	269°		15.5°	+31.4°	
$\text{C}_{11}\text{H}_{22}\text{O}_2$	Undecylic acid	212°	+28.0°			12.2°
$\text{C}_{12}\text{H}_{24}\text{O}_2$	Lauric acid	225°		12.5°	43.6°	
$\text{C}_{13}\text{H}_{26}\text{O}_2$	Tridecylic acid	236°	40.5°			10.4°
$\text{C}_{14}\text{H}_{28}\text{O}_2$	Myristic acid	248°		11.6°	54.0°	
$\text{C}_{15}\text{H}_{30}\text{O}_2$	Pentadecylic acid	257°	52.1°			9.1°
$\text{C}_{16}\text{H}_{32}\text{O}_2$	Palmitic acid	268°		9.9°	63.1°	
$\text{C}_{17}\text{H}_{34}\text{O}_2$	Margaric acid	277°	62.0°			7.0°
$\text{C}_{18}\text{H}_{36}\text{O}_2$	Stearic acid	287°		7.4°	70.1°	
$\text{C}_{19}\text{H}_{38}\text{O}_2$	Nonadecylic acid	298°	69.4°			5.1°
$\text{C}_{20}\text{H}_{40}\text{O}_2$	Arachidic acid	—			75.2°	

This peculiar distribution of the carboxylic acids into two series, one with even numbers of carbon atoms, the other with odd numbers, can be recognized not only in connection with melting points, but also, in part, in the chemical and biological properties. Thus, those acids with an even number of carbon atoms give acetone on passing through the liver (Embsden), the others do not, and a similar oscillation is observed, for example, in the dissociation constants of different homologous carboxylic acids (particularly unsaturated ones, Fr. Fichter).

The fatty acids possess an acidic nature. Their carboxyl hydrogen atom can be replaced by a metal. In aqueous solution they are partially dissociated, but the dissociation is very small compared with that of the mineral acids.

The dissociation, and hence the strength of an acid, are usually expressed by the dissociation constant k . This constant is derived from the "dilution law", which gives the relation between the dissociation of a weak acid and its dilution. It is derived from the following considerations:

Suppose 1 gm-mol of acid is dissolved in v litres, and α gm-mol of it is dissociated:



The concentration of the ions is then $\frac{\alpha}{v}$, and that of the undissociated acid $\frac{1-\alpha}{v}$.

Applying the law of mass action to the above equilibrium:

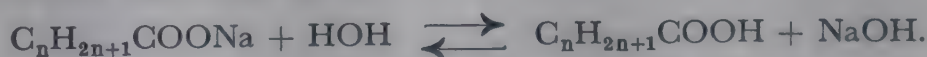
$$\frac{[\text{H}^{\cdot}][\text{C}_n\text{H}_{2n+1}\text{COO}']}{[\text{C}_n\text{H}_{2n+1}\text{COOH}]} = \frac{\frac{\alpha^2}{v^2}}{\frac{1-\alpha}{v}} = k; \quad k = \frac{\alpha^2}{v(1-\alpha)}.$$

The dissociation constant, k , is sometimes multiplied by 100, and is then denoted by K . The value of K for the first carboxylic acids (at 25°) is given in the following table:

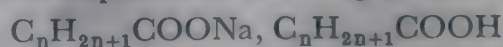
	K
Formic acid	0.0214
Acetic acid	0.0018
Propionic acid	0.0014
Butyric acid	0.0015
Valeric acid	0.0016
Caproic acid	0.00146
Oenanthic acid	0.00146

Compared with hydrochloric acid, N/10 acetic acid is about one-hundredth as much dissociated, and is correspondingly weaker.

The alkali salts of weak acids are always considerably hydrolysed in aqueous solution. This also occurs for the salts of the very weak higher fatty acids. Their solutions therefore react alkaline:

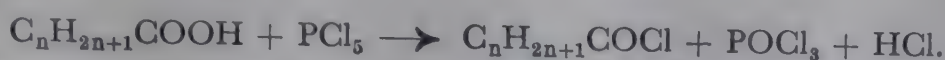


The carboxylic acids are strongly associated, and even above their boiling points have a molecular weight twice as great as that corresponding to their simple molecular formula. The associating power of water is therefore found again not only in its monoalkyl derivatives (alcohols) but also in the monoacyl derivatives, the carboxylic acids. It is because the fatty acids can exist in the dimeric form that they are capable of forming acid salts of the formula:



CHEMICAL PROPERTIES OF THE FATTY ACIDS. The hydroxyl group of the car-

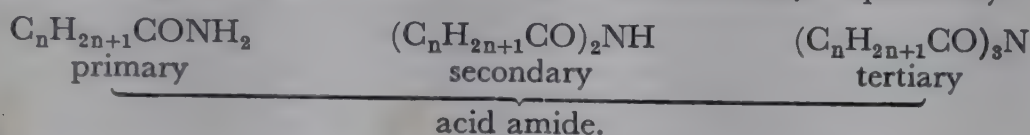
boxylic acids is very reactive, and can be replaced by many other atoms or groups, e.g. Cl, SH, NH₂, —NHNH₂, N₃, —NHOH. Thus, the phosphorus halides convert the fatty acids into *acid chlorides*, $C_nH_{2n+1}C(=O)Cl$, *acid bromides*, $C_nH_{2n+1}C(=O)Br$, and *acid iodides*, $C_nH_{2n+1}C(=O)I$.



Phosphorus pentasulphide produces *thio-acids*, $C_nH_{2n+1}COSH$, colourless, low-melting compounds, with an unpleasant smell. Their alkali salts are soluble in water, whilst those of the heavy metals are not. *Dithio-acids*, $C_nH_{2n+1}CSSH$ are also known. They are prepared, however, not from the carboxylic acids, but from alkylmagnesium salts, which react with carbon disulphide:



The replacement of the hydroxyl group of carboxylic acids by ammonia radicals gives the *acid amides*. The best known and the most frequently used are the primary amides: there are, however, secondary and tertiary amides in addition, which may be regarded as di- and triacylated ammonia, respectively:



The primary acid amides are made from ammonia and the acid chlorides, or esters:



Analogous compounds are produced by the action of the acid chlorides or esters on hydrazine. They are called the *acid hydrazides*, $C_nH_{2n+1}CONHNH_2$. Nitrous acid converts them into the *acid azides*, $C_nH_{2n+1}CON_3$:



The *alkylhydroxamic acids*, $C_nH_{2n+1}CO \cdot NHOH$, can be obtained by the action of hydroxylamine on the esters of the carboxylic acids:



For Kolbe's synthesis of hydrocarbons by electrolysis of the salts of fatty acids see p. 29. The addition of alkylmagnesium salts to the carboxylic esters, giving tertiary alcohols, has already been mentioned. For the syntheses of aldehydes and ketones from carboxylic acids, see pages 159 and 173.

The carboxyl group is very resistant to reduction. In order to reduce it to the methyl group it is necessary to heat for a long time with hydriodic acid and phosphorus, and even then the reduction often does not proceed very smoothly. Some of the higher fatty acids respond better to this treatment. Carboxylic acids can also be directly reduced by hydrogen under high pressure, and at high temperatures with the use of catalysts (Cu, Ni, Co) (Schrauth, Norman). By means of these processes higher primary alcohols are nowadays industrially produced, chiefly from higher fatty acids, and are used in the manufacture of detergents (fatty alcohol sulphonates, see p. 113).

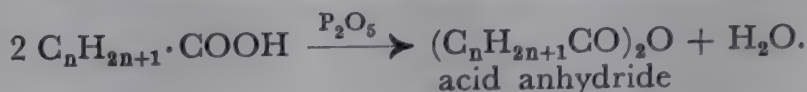
The esters of the carboxylic acids are more easily reduced, giving up to 70 and 80 per cent of primary alcohols when treated with sodium and alcohol, (Bouveault and Blanc):



The elegant method of reduction for carboxylic acid esters which makes use of lithium aluminium hydride is referred to on page 83.

The reduction of the acid chlorides to aldehydes and primary alcohols by means of hydrogen in the presence of a catalyst is also possible (Rosenmund).

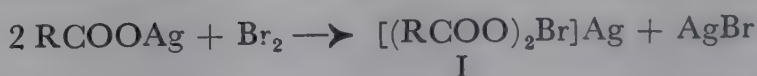
By elimination of water (e.g. by means of phosphorus pentoxide) the acids are converted into the *acid anhydrides*, important compounds, which are often used in acylations:



Decarboxylation of carboxylic acids and their conversion into other types of compounds can be effected in various ways. In the section on "Saturated hydrocarbons", their conversion into hydrocarbons by the methods of Dumas and Kolbe was described (p. 29); the A. W. Hofmann and Curtius methods of converting them into amines were dealt with in the chapter on "Amines" (p. 130). It is also possible to obtain alkyl halides from carboxylic acids. When their silver (or mercury, or potassium) salts react with chlorine or bromine, they often give good yields of alkyl halides, carbon dioxide being liberated in the process:



Compounds of type I may possibly be assumed to be intermediate products in this reaction:

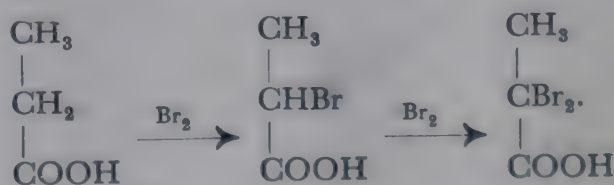


Amongst the compounds obtained by this method are undecyl bromide from lauric acid, and octamethylene bromide from sebacic acid (Lüttringhaus, Hunsdiecker, and others).

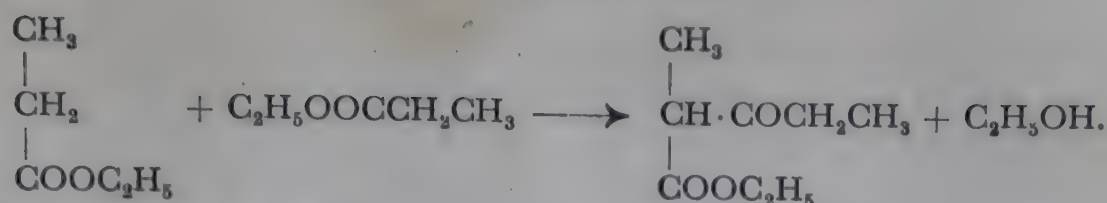
The silver salts of the carboxylic acids react with iodine in a similar manner. In this reaction, iodoacyl compounds are first formed, $\text{I}(\text{OCOR})_3$, and when these are heated with an excess of iodine they split up into the alkyl iodide and carbon dioxide. The mechanism of this reaction is not yet clear (J. W. H. Oldham, A. R. Ubbelohde).

The *esters of the carboxylic acids*, amongst which are many naturally occurring substances, will be fully dealt with later.

Mention may be made here of the effect exerted by the carboxyl group on the reactivity of the alkyl radical. The hydrogen atoms attached to the adjacent α -carbon atom are activated by the carboxyl group. They enter into reaction much more readily than the other hydrogen atoms of the alkyl residue. For example, they are substituted by halogens:



Moreover, the α -CH₂ group can condense with esters of carboxylic acids under the influence of sodium:

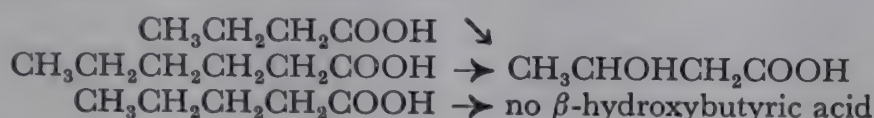


(For the mechanism of this condensation, see acetoacetic ester).

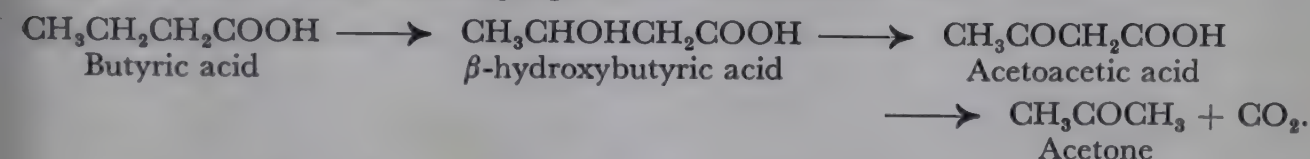
Biological experiments first indicated that the β -position of a fatty acid could also be the primary point of attack in a reaction. Thus, it has been shown that the fatty acids are usually oxidized in the organism at the β -position, and where this is impossible owing to the particular constitution of the compound, they remain unattacked¹ (F. Knoop, Friedmann, Embden, Baer and Blum).

Thus benzoic acid, $\text{C}_6\text{H}_5\text{COOH}$, and phenylacetic acid, $\text{C}_6\text{H}_5\text{CH}_2\text{COOH}$, are not attacked, whilst phenylpropionic acid, $\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{COOH}$, is converted into benzoic acid, phenylbutyric acid, $\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{CH}_2\text{COOH}$, into phenylacetic acid, and phenylvaleric acid, $\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{COOH}$, into phenylpropionic acid.

Furthermore, the organism of diabetic persons is able to convert butyric acid, $\text{CH}_3\text{CH}_2\text{CH}_2\text{COOH}$, and caproic acid, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{COOH}$, into β -hydroxybutyric acid, but not valeric acid:

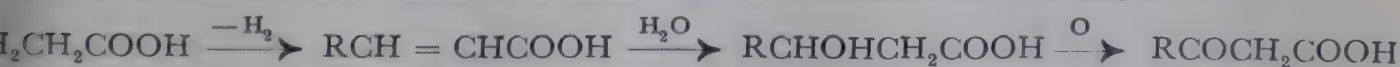


While such experiments put the biological importance of β -oxidation beyond doubt, later experiments of H. D. Dakin have shown that the fatty acids can also be oxidized in the β -position *in vitro*. This can be done with 3 per cent hydrogen peroxide. Butyric acid is thus converted into β -hydroxybutyric acid, and, by further action of the oxidizing agent, into acetoacetic acid:



These reactions show that the β -position of the fatty acids is specially sensitive towards certain oxidizing agents, and is attacked preferentially by these reagents. This is of outstanding importance in connection with the elucidation of biological oxidation processes.

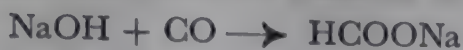
The course of the so-called β -oxidation has, however, not yet been completely elucidated. It is possible that the primary process consists in a dehydrogenation of the fatty acid in the α,β -position, after which water adds on to the α,β -unsaturated carboxylic acid:



Evidence for this course of the reaction is, for example, that α,β -unsaturated acids are converted by the action of fungi into the same methyl ketones, that are also obtained by decarboxylation of the β -ketocarboxylic acids originating from them. The view that the initial step is a dehydrogenation in the α,β -position appears, moreover, to be supported by the fact that in the rat organism β,γ -dideuterobutyric acid (i.e. butyric acid containing a *heavy* hydrogen atom both in the β - and γ -position) is chiefly excreted as deuterio- β -hydroxybutyric acid, whereas α,β -dideuterobutyric acid under analogous conditions, loses its deuterium content almost entirely.

¹ See FRANZ KNOOP, *Oxydationen im Tierkörper. Ein Bild von den Hauptwegen physiol. Verbrennung*, Stuttgart, (1931).

and at a temperature of 120–150°. Sodium formate is produced quantitatively:



This process, which is due to the work of Berthelot and V. Merz, has been so much improved by M. Goldschmidt and others that formic acid derivatives are now cheap products, and have found many technical applications.

The direct combination of carbon monoxide and water to yield formic acid, is possible only under elevated pressures, at medium temperatures (e.g. 200–300°), and in the presence of catalysts such as HBF_4 , H_2SO_4 , H_3PO_4 , etc. Even then the attainable equilibrium lies strongly in favour of carbon monoxide and water, so that this process has no technical importance at present.

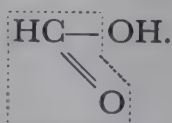
The manufacture of formic acid by oxidation of methyl alcohol has again become of interest, since the latter is now readily available by reduction of carbon monoxide.

PROPERTIES. Anhydrous formic acid is a clear, mobile liquid with a very pungent smell. It is strongly corrosive, and raises blisters on the skin. It is the strongest fatty acid (see table of dissociation constants, p. 194). Its boiling point is 100.6° (760 mm). It is therefore impossible to obtain formic acid free from water by fractional distillation. Technically, anhydrous formic acid is obtained by the decomposition of dry sodium formate with concentrated sulphuric acid, the acid being diluted with anhydrous formic acid to reduce to a minimum the decomposition of the formic acid by the sulphuric acid.

The action of dry hydrogen sulphide on lead formate is likewise useful for obtaining small quantities of the anhydrous acid:



Formic acid enters into some chemical reactions which are not given by its higher homologues. This is due to the fact that it contains an aldehyde group:



In several reactions its aldehydic nature comes to the forefront. Thus, formic acid acts like an aldehyde in being a strong antiseptic, and a powerful reducing agent. It reduces ammoniacal silver nitrate solution to silver on warming.

Under the influence of catalysts (rhodium, ruthenium, iridium) it decomposes, even at ordinary temperatures, into hydrogen and carbon dioxide:



On warming with concentrated sulphuric acid it is decomposed into carbon monoxide and water.



The salts of formic acid, the *formates*, are decomposed when heated in the dry state. Some, like the zinc salt, give formaldehyde (q.v.) and zinc carbonate, but the alkali salts on rapid heating above 400° give chiefly oxalates. This process can be used for the technical preparation of oxalic acid:



Since formic acid has become a cheap substance it has been used on a large scale in the textile industry for the preparation of mordants and for the dyeing of wool and cotton

fabrics from an acid bath. It is often used in place of acetic acid, and partly of sulphuric acid, which were formerly employed for this purpose. It has the advantage over the latter of not injuring the fabric in any way. In the preparation of leather, formic acid is used for removing lime from the leather. Its antiseptic properties are made use of when it is employed for the preserving of fruit juices, the cleansing of casks, etc.

Acetic acid. Acetic acid was known in the form of sour wine in very early times. Pliny mentions that Cleopatra enjoyed a drink that was made by dissolving pearls in vinegar. Concentrated acetic acid was first prepared about two hundred years ago.

This acid is extremely widely spread in the plant kingdom. Plants contain it partly in the free form, but generally as esters, in which it is combined with various alcohols. It has also often been detected in animal secretions.

A large number of micro-organisms, fungi, and moulds, have the property of converting organic substances into acetic acid. The compound is therefore found in sour milk, and cheese, and is formed particularly in the "souring" of alcoholic liquids. In this way, much vinegar was made from wine in former years. In this process the necessary acetic fungi ("mother of vinegar") were introduced into the alcoholic liquid, and the latter was allowed to stand for some time in a warm place, the alcohol being oxidized to acetic acid (Orléans process). The oxidizing agent is atmospheric oxygen. The acetic fungi contain an enzyme, "alcoholoxidase", which catalytically accelerates the process of oxidation (Buchner).

The mechanism of this reaction has been largely elucidated by the work of Wieland. It has been shown that the acetic bacteria oxidize the alcohol to acetaldehyde, the hydrate of which is converted directly into acetic acid by enzymatic dehydrogenation. According to Neuberg an aldehyde mutase also plays a part in this transformation, converting the acetaldehyde into equal parts of acetic acid and alcohol.

More rapid than the Orléans process, but depending on the same principle is the "quick vinegar process" of Schützenbach. The oxidation of dilute (5–10 per cent) alcoholic solutions is carried out in "acetic acid vats". The dilute alcohol is allowed to trickle over wood shavings, and air is forced through the liquid that has reached the lower parts, so that the alcohol comes into intimate contact with the air, and is rapidly oxidized under the influence of the acetic fungi present. After two or three repetitions of the process the oxidation of the alcohol is complete.

At present most of the acetic acid used is, however, produced in other ways. As already mentioned in dealing with methyl alcohol above, it is found in large quantities amongst the products of the dry distillation of wood ("pyroligneous acid"). It is "fixed" by lime, the crude calcium acetate ("grey" calcium acetate) is separated, and decomposed into calcium sulphate and acetic acid by treatment with sulphuric acid:



Acetic acid is also prepared by a process already described and continuously increasing in importance, from acetylene (see p. 70–1), which is converted into acetaldehyde and "carbide acetic acid" is at present on the market in addition to "wood acetic acid". The oxidation of acetaldehyde is carried out technically with atmospheric oxygen, with acetic acid itself or various metal oxides (those of iron, manganese, vanadium, uranium, etc.) acting as catalysts.

Pure acetic acid is a clear liquid with a pungent smell, and is corrosive.

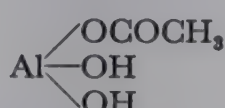
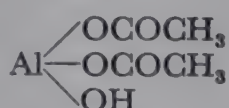
If anhydrous it freezes at 16° to ice-like crystals, which has led to the name "glacial acetic acid". It boils at 118° . Above its boiling point, the vapour density is considerably higher than that corresponding to the monomolecular formula. The acid is still associated at this temperature, and breaks down into single molecules completely only at much higher temperatures.

The maximum density of aqueous solutions of acetic acid occurs with a solution containing 77 per cent of the acid (density = 1.07 at 20°). This composition corresponds to the monohydrate, so that it appears that the ortho-form of acetic acid, $\text{CH}_3\text{C}(\text{OH})_3$, is present at the density maximum. Anhydrous acetic acid has a density of 1.05 at 20° .

Besides its use for domestic purposes, acetic acid is used in the synthesis of perfumes, dyes, and acetone (see p. 176), for the manufacture of cellulose acetate, and acetate salts, and also in the dyeing industry and in printing. Its technical importance is thus considerable.

Of the salts of acetic acid, the *acetates*, those of the alkali metals are readily soluble in water and are strongly dissociated. Anhydrous sodium acetate, a very hygroscopic substance, is often used as a dehydrating agent in organic syntheses.

The acetates of the trivalent metals, iron, aluminium, and chromium, correspond to the formula $\text{M}^{\text{III}}(\text{OCOCH}_3)_3$. They are soluble in water, but if heated with it, they are hydrolysed to give insoluble basic salts, which can be represented by the formulæ:



These are important in connection with the mordanting of fabrics. The fabric to be mordanted is steeped in a solution of aluminium or chromium acetate, and is hung up to dry in hot water vapour. The acetate is thus converted into the insoluble basic salt and the hydroxide of the metal. These remain mechanically attached to the fibre, and combine with certain dyes to form insoluble "lakes". Such mordanted colours are usually very fast.

The property of the acetates of the three *trivalent* elements mentioned above of forming insoluble basic acetates on heating with water is made use of in analysis for the separation of these metals from the *divalent* metals. The acetates of the latter are unaffected by warming their solutions.

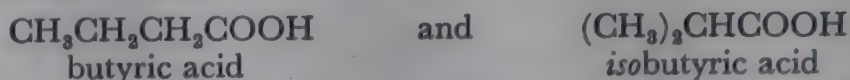
Aluminium acetate, *liquor aluminii acetici*, is a valuable antiseptic and astringent.

The sweet tasting, neutral lead acetate, $\text{Pb}(\text{OCOCH}_3)_2 \cdot 3 \text{H}_2\text{O}$, *sugar of lead*, is used in the manufacture of the pigments white lead and chrome yellow. A solution of basic lead acetates, $\text{Pb}(\text{OH})_2 \cdot \text{Pb}(\text{OCOCH}_3)_2$ and $2 \text{Pb}(\text{OH})_2 \cdot \text{Pb}(\text{OCOCH}_3)_2$, is used for a similar purpose. This solution is also used in medicine as a lotion for injuries and burns. Green copper acetate $\text{Cu}(\text{OCOCH}_3)_2$ was formerly used for the pigment Schweinfurter Green.

Propionic acid, $\text{CH}_3\text{CH}_2\text{COOH}$. This acid is probably most conveniently prepared by the oxidation of propyl alcohol by means of chromic acid. It is formed in small quantities in various fermentation processes, and is contained in crude "pyroligneous acid".

Propionic acid has a pungent smell. It is readily soluble in water, but can be thrown out of solution by the addition of easily soluble salts, such as calcium chloride. In this it differs from acetic acid. It boils at 140° (760 mm), and melts at -21.5° .

Butyric acids. The fatty acids containing four carbon atoms occur in two structurally isomeric forms:



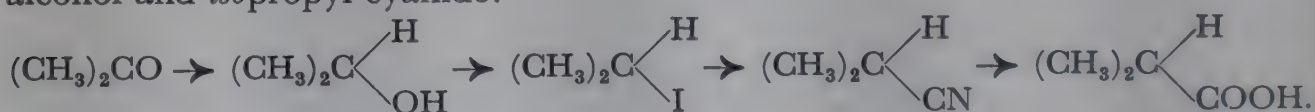
BUTYRIC ACID is found as its glyceryl ester in cow's butter (Chevreul), and as its hexyl and octyl esters in plant and animal oils. In the free state it is present in the juice of muscle, in perspiration, and in the fæces of animals.

Butyric acid can be formed by the bacterial fermentation of starch, sugar, glycerol, and lactates. These processes are also used for the technical production of butyric acid. It is convenient to work as far as possible with pure cultures of butyric acid bacteria (*Bac. butylicus*, *Granulobacter*, etc.) in order to prevent secondary fermentations which lead to other products. By the addition of calcium carbonate the butyric acid is neutralized as it is formed. By similar processes it is formed in foodstuffs (Limburg cheese, Sauerkraut, etc.).

Butyric acid is a colourless liquid, which has a pungent smell in the concentrated state, but when diluted smells of perspiration. Its boiling point is 162° , and its melting point -5.5° . It is miscible with water, but is salted out on addition of salts. It is volatile in steam. Calcium butyrate, $(\text{CH}_3\text{CH}_2\text{CH}_2\text{COO})_2\text{Ca}$, H_2O , is characterized by the fact that it is less soluble in hot water than in cold. It can easily be purified on account of this property, and can also be separated from calcium isobutyrate, which behaves normally, i.e. is more soluble in hot water than in cold.

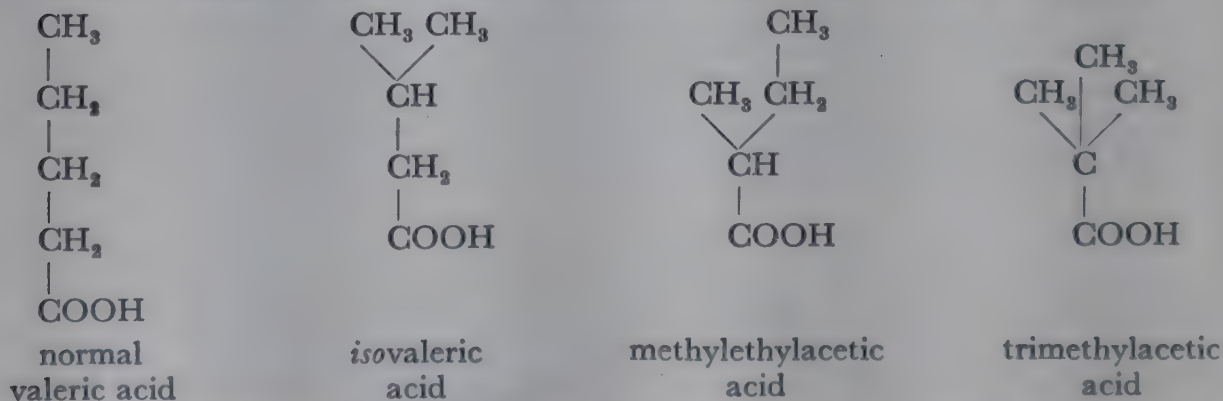
Butyric acid is used in the preparation of butyric esters, which, on account of their fruit-like smells, are used in perfumery. Butyric acid is also used in tanning for removing lime from leather.

ISOBUTYRIC ACID is found in the free state in the carob bean, and in the essential oil of *Arnica montana*, and as ethyl isobutyrate in Roman camomile oil, and croton oil. It is most conveniently prepared from acetone, through isopropyl alcohol and isopropyl cyanide:



The boiling point of isobutyric acid is 154° , and its melting point -79° .

Valeric acids. The four valeric acids required by theory are known:



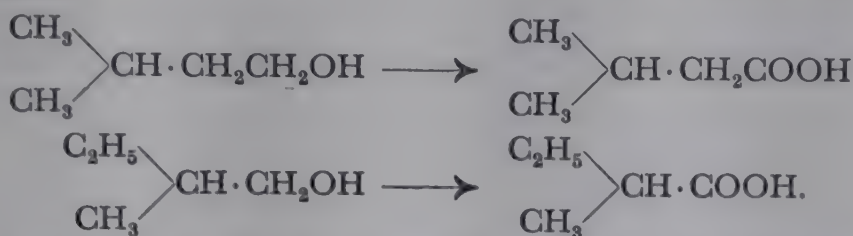
NORMAL VALERIC ACID can be obtained by the oxidation of normal primary amyl alcohol, or by the reduction of lævulinic acid with sodium amalgam:



It is found in small quantities in pyroligneous acid, and in the water from lignite distillation. It is formed with other fatty acids in the oxidation of stearic acid and castor oil, and by the bacterial decomposition of calcium lactate.

ISOVALERIC ACID is found in the free state in larger quantities in valerian root, and as an ester in various essential oils. It can be extracted from valerian root by distillation in steam. Medicinal valeric acid from valerian contains, in addition to *isovaleric* acid, some of the optically active methylethylacetic acid, which gives the preparation a slight rotation.

Isovaleric acid can be obtained synthetically by the oxidation of inactive fermentation amyl alcohol, and methylethylacetic acid can be obtained in a similar way from optically active amyl alcohol:



Isovaleric acid is used for the synthesis of some medicinal preparations.

TRIMETHYLACETIC acid is obtained by the oxidation of pinacolin:



Normal valeric acid has b.p. 185°, m.p. —58°; *isovaleric* acid, b.p. 174°, m.p. —51°; methylethylacetic acid, b.p. 177°; trimethylacetic acid, b.p. 163°, m.p. 35°.

Higher fatty acids. Of the higher fatty acids the normal primary compounds are known especially well. Many of them are naturally occurring products. They are found as esters of the lower alcohols in the essential oils of plants, as glycerides

		Occurrence (incomplete)
C ₅ H ₁₁ COOH	Caproic acid	In the butyric acid fermentation of sugar. As an ester in palmarosa oil.
C ₆ H ₁₃ COOH	Oenanthic acid	As an ester in calamus oil.
C ₇ H ₁₅ COOH	Caprylic acid	As a glyceride in cow's butter, in coconut oil. As an ester in wine.
C ₈ H ₁₇ COOH	Pelargonic acid	In the volatile oil of <i>Pelargonium roseum</i> . In fusel oil from beet and potatoes.
C ₉ H ₁₉ COOH	Capric acid	As a glyceride in cow's butter, in coconut oil, in Limburg cheese. As an ester in wine.
C ₁₁ H ₂₃ COOH	Lauric acid	As a glyceride in laurel oil, in coconut oil, in pichurim beans, in spermaceti.
C ₁₃ H ₂₇ COOH	Myristic acid	As a glyceride in nutmeg oil, in coconut oil, in the seeds of <i>Virola venezuelensis</i> .
C ₁₅ H ₃₁ COOH	Palmitic acid	As a glyceride in very many animal and vegetable fats. As an ester in some waxes.
C ₁₇ H ₃₅ COOH	Stearic acid	As a glyceride in very many animal and vegetable fats.
C ₁₉ H ₃₉ COOH	Arachidic acid	As a glyceride in peanut oil (<i>Arachis hypogaea</i>), in rape oil, cacao-butter, and macassar oil.
C ₂₀ H ₄₁ COOH	Eicosanecarboxylic acid	In Japanese wax, peanut oil, etc.
C ₂₁ H ₄₃ COOH	Behenic acid	As a glyceride in rape oil and peanut oil.
C ₂₃ H ₄₇ COOH	Lignoceric acid	In peanut oil (?), and wood-tar.
C ₂₅ H ₅₁ COOH	Cerotic acid	As an ester in beeswax and other kinds of wax, in the sweat of sheep.
C ₂₉ H ₅₉ COOH	Melissic acid	In Carnauba wax and beeswax.
C ₃₂ H ₆₅ COOH	Psyllastearic acid	In the wax of the plant-louse <i>Psylla alni</i> .

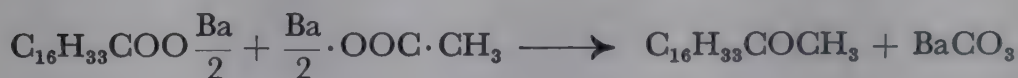
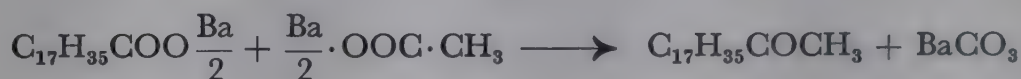
in fats and oils (see p. 192), and as esters of the higher monohydric alcohols in the waxes (see p. 108). The names and occurrence of some of them are given above. Of the acids containing more than ten carbon atoms, those with even numbers of carbon atoms are met with predominantly, if not exclusively in nature.

The most abundant of these acids are palmitic and stearic acids, of which the glycerides, with those of oleic acid (see p. 208) form the major part of most fats and oils. They crystallize — like the other higher fatty acids — in wax-like leaflets. They are almost insoluble in water, but dissolve in many organic solvents.

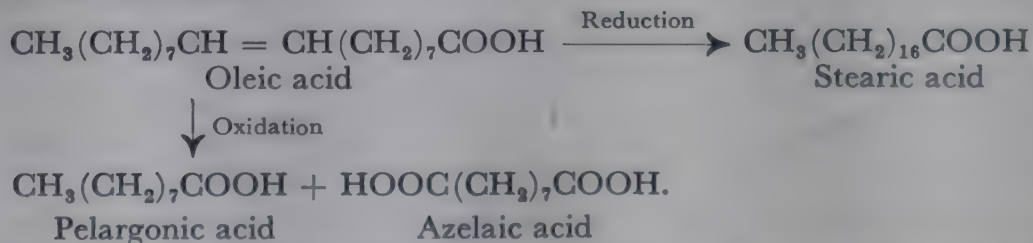
Of their salts the sodium and potassium salts are specially important. They are the *soaps*. They will be more fully considered in connection with fats.

The separation of mixtures of the higher fatty acids presents great experimental difficulties. Various processes have been recommended, but they are often only applicable to special cases. Thus, if a little magnesium acetate is added to a concentrated alcoholic solution of fatty acids, the magnesium salts of the higher fatty acids which are difficultly soluble in alcohol are first precipitated. Another method of separation is based on the fractional distillation of the esters of the fatty acids, and a third on the fractional neutralization with alkalis, the lower fatty acids, which are stronger, being neutralized before the higher ones.

The normal structure of stearic acid can be proved in various ways. Krafft has broken down stearic acid systematically to capric acid, which is known to possess a normal carbon chain by synthesis, in the following way:



The course of this decomposition will only agree with the normal structure for stearic acid. The following considerations lead to the same result: *Oleic acid*, $\text{C}_{17}\text{H}_{33}\text{COOH}$, can be converted into stearic acid by reduction, and by oxidation gives pelargonic acid and azelaic acid. The two latter acids are known to have the normal structure by synthesis. Thus both oleic and stearic acids must have a straight carbon chain:



In plants and animals, however, some higher carboxylic acids with branched carbon chains, have been detected, e.g. *d*-14-methylpalmitic acid in wool fat and *l*-10-methylstearic acid (tuberculo-stearic acid) in tubercle bacilli.

Monobasic unsaturated acids with ethylenic linkages; acrylic or oleic acid series, $C_nH_{2n-1}COOH$

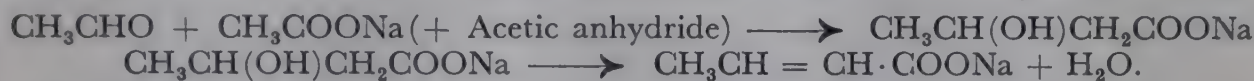
Monobasic unsaturated carboxylic acids with ethylenic linkages are frequently met with in nature, such as *oleic acid*, $C_{17}H_{33}COOH$, in oils and fats, *crotonic acid*, C_3H_5COOH , in croton oil, *angelic acid*, C_4H_7COOH , and the isomeric *tiglic acid* in the oil of the Angelica root and Roman camomile oil, *erucic acid*, $C_{21}H_{41}COOH$, in oil of mustard seed.

The following processes may be used for the *synthesis* of these compounds:

1. The oxidation of unsaturated aldehydes by oxidizing agents which do not attack the double bond (e.g. silver oxide):

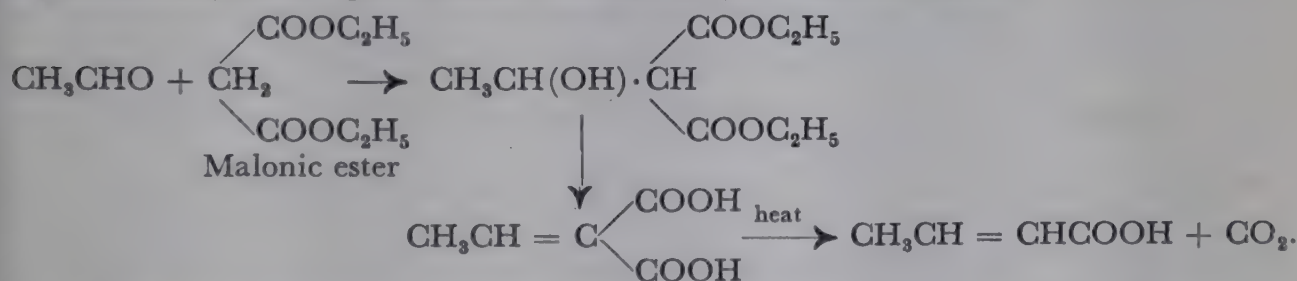


2. Condensation of aldehydes with the sodium salts of carboxylic acids, under the influence of acid anhydrides. This reaction, which is called Perkin's reaction, is one of the most useful syntheses for unsaturated acids. The primary process is an aldol condensation. In the second stage water is eliminated and the double bond is formed:



The sodium salts of the higher carboxylic acids will also combine with aldehydes in this way, the reaction always taking place in the α -position, i.e. at the CH_2 group next to the carboxyl group.

3. The malonic ester synthesis. This is closely related to the Perkin synthesis and depends upon the fact that aldehydes will condense with diethyl malonate in the presence of glacial acetic acid, giving products which, on hydrolysis followed by decarboxylation, give unsaturated acids (see malonic acid):



4. Hydroxycarboxylic acids and halogen substituted carboxylic acids, especially those with the hydroxyl group or the halogen in the β -position give compounds of the acrylic acid series by elimination of water or halogen hydride, respectively:



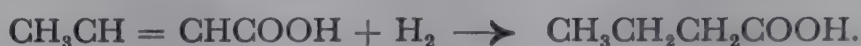
The water can be removed by distillation, or by the action of sulphuric acid, for example, and the halogen hydride can be removed by alkalis.

PROPERTIES: The lower members are easily soluble in water, but the solubility decreases rapidly as the series is ascended. There is often a characteristic difference in the melting points of the saturated and unsaturated acids. Whilst the saturated acids with ten or more carbon atoms are solid at ordinary temperatures, the unsaturated oleic acid, $C_{18}H_{34}O_2$, for example, only freezes when cooled and melts again at 14° .

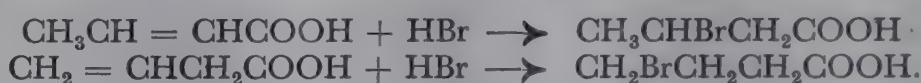
The position of the double bond is of paramount importance for the strength

of the unsaturated acids (Fr. Fichter). In general, the members of the acrylic acid series are more strongly dissociated than those of the saturated series. This is particularly the case if the double bond occurs between the β - and γ -carbon atoms, whilst the $\Delta^{\alpha,\beta}$ -acids, and the $\Delta^{\gamma,\delta}$ -acids have somewhat smaller dissociation constants (another example of oscillation of properties).

The ethylenic linkage introduces new possibilities of reactivity into the unsaturated acids, compared with the saturated ones. The former are capable of entering into all those addition reactions which have been previously mentioned as characteristic of ethylenic compounds. Thus the members of the acrylic acid series readily take up halogens, halogen hydrides, and hydrogen. The $\Delta^{\alpha,\beta}$ -acids are the most easily reduced, a fact connected with the existence in these compounds of a conjugated system of double bonds:



In the addition of the halogen hydrides to the $\Delta^{\alpha,\beta}$ -acids, the halogen atom enters in the β -position, and in the case of the $\Delta^{\beta,\gamma}$ -acids usually in the γ -position, though the course of the latter reaction is influenced by external conditions (addition of solvent, etc.) and possibly by alkyl substituents present at the double bond:



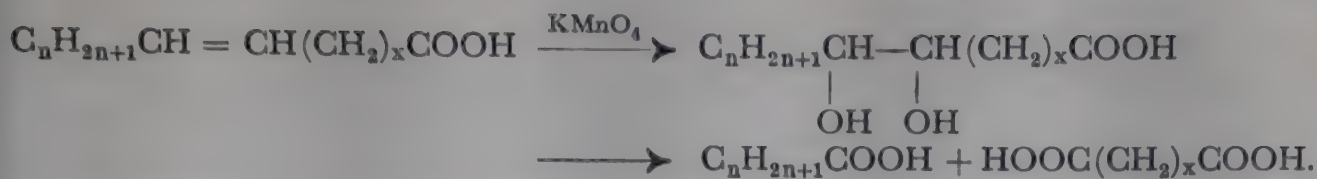
The phenomenon investigated by Fittig, that the double bond in the unsaturated acids can migrate within the hydrocarbon radical is of considerable interest. Thus, the $\Delta^{\beta,\gamma}$ -acids, on heating with alkali, are partially transformed into $\Delta^{\alpha,\beta}$ -acids, and the latter, on treatment with alkali, are converted reversibly into the $\Delta^{\beta,\gamma}$ -acids, so that an equilibrium is set up. The more accurate investigation of this process has shown that both $\Delta^{\beta,\gamma}$ - and $\Delta^{\alpha,\beta}$ -acids take up water under these conditions, giving β -hydroxy-acids. The latter lose water again and are converted into a mixture of $\Delta^{\beta,\gamma}$ - and $\Delta^{\alpha,\beta}$ -acids, in which the $\Delta^{\alpha,\beta}$ -acid predominates:



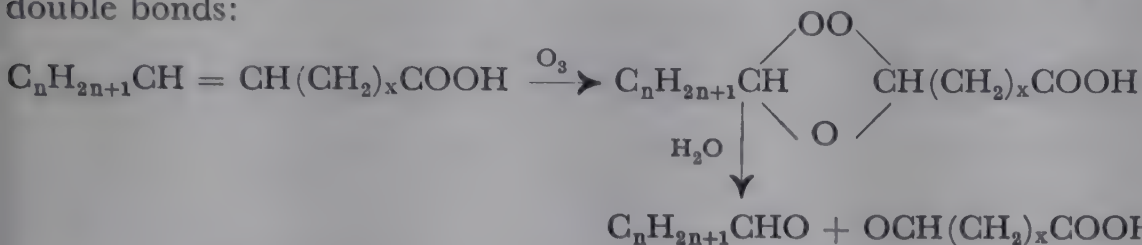
This process makes it clear that in the determination of the position of the double bond in unsaturated acids, only those reactions can be used which are not accompanied by a displacement of the double bond. Thus, fusion with alkali, which was formerly used for this purpose and which converts acrylic acid into smaller fission products, should not be employed because it usually breaks the unsaturated acid between the α - and β -positions, irrespective of the position of the double bond. Thus, oleic acid breaks down smoothly on fusion with alkali into palmitic acid and acetic acid, although its double bond is between the ninth and tenth carbon atoms:



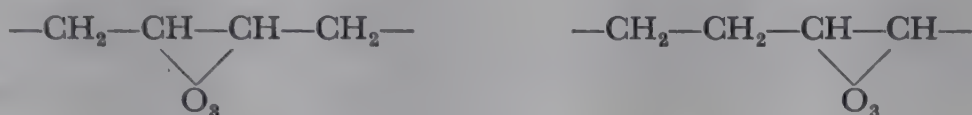
The oxidation of the unsaturated carboxylic acids with potassium permanganate or ozone is of special value in determining their constitution. In the first case two hydroxyl groups first add on across the double bond. The dihydroxy-acid formed is further oxidized at the carbon atoms attached to the hydroxyl groups, forming two acids, the fission taking place where the double bond originally was:



The reaction between the acrylic series of acids and ozone is similar. It too is very useful for determining the structure of the acids and the position of the double bonds:

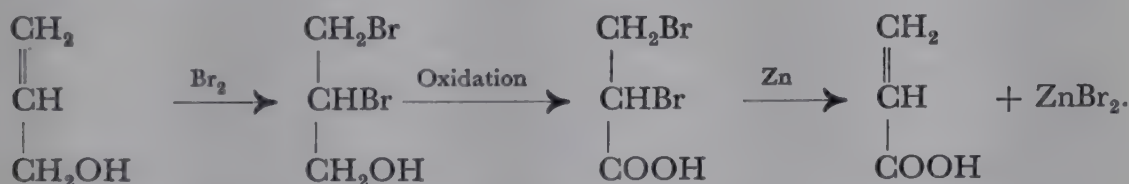


It should be mentioned, however, in this connection that the fission with ozone occasionally gives misleading results. Thus, the ozonization of cleic acid (see p. 204) gives in addition to azelaic acid not only pelargonic acid but also lower and higher homologues, if only in small amounts. They owe their formation to a wandering of the ozone group in the ozonized molecule:



Fission of the carbon chain *next to* the double bond has been repeatedly observed to a small extent in other cases of ozonization.

ACRYLIC ACID, $\text{CH}_2=\text{CH}\cdot\text{COOH}$. In addition to being obtained by the oxidation of acrolein, acrylic acid can be obtained from allyl alcohol by the following method:



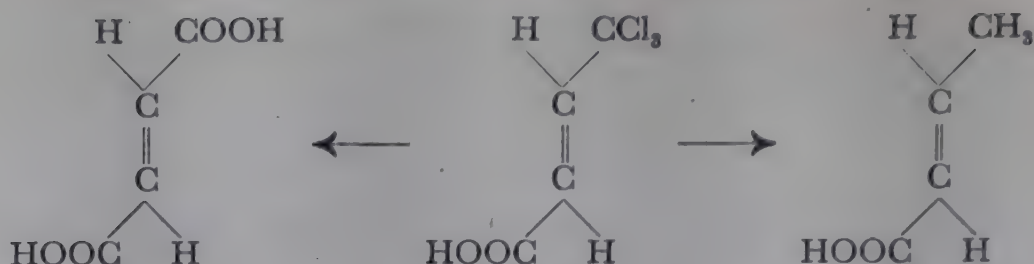
It is a liquid with a pungent smell, which boils at 140° , and melts at 13° . It tends to polymerize.

CROTONIC AND ISOCROTONIC ACIDS, $\text{CH}_3\cdot\text{CH}=\text{CH}\cdot\text{COOH}$. Many of the homologues of acrylic acid exist in stereoisomeric forms. Their isomerism depends on the different positions taken up by the substituents with respect to the double bond. It is thus a special case of the geometrical isomerism shown by ethylenic compounds (see p. 48), a *cis-trans* isomerism. For crotonic and *isocrotonic* acids the two following formulæ come into consideration:



The identity of their structure follows from the fact that both compounds give *n*-butyric acid on reduction and oxalic acid on oxidation.

Crotonic acid is very probably the *trans*-form, and *isocrotonic* acid the *cis*-form. This follows primarily from experiments carried out by v. Auwers, by which crotonic acid was shown to be related to fumaric acid by reactions which avoided any possibility of change of configuration:



The physical properties of the two isomerides also agree with this. The more stable form of a pair of geometrical isomerides usually melts at a higher temperature, has a smaller heat of combustion, and smaller solubility, properties which are related to the symmetry relationships of the molecule. The symmetrically constructed *cis*-isomers show a tendency to pass into the unsymmetrical *trans*-forms, and are therefore richer in energy, and correspondingly more unstable. (See also maleic and fumaric acids).

Crotonic acid is found in croton oil. It is a crystalline substance, melting at 72° , and boiling at 180° . *Isocrotonic* acid melts at 15.5° , and boils at 169° . The latter is the more labile form, since, on heating above 100° it is partly converted into crotonic acid.

ANGELIC ACID and TIGLIC ACID, $\text{CH}_3 \cdot \text{CH} = \text{C}(\text{CH}_3) \cdot \text{COOH}$. These two compounds are also geometrical isomerides, and have the formulæ:



Angelic acid is the labile, and tiglic acid the more stable form, since the former, on warming or treatment with sulphuric acid, is converted into the latter.

Angelic acid is found as an ester in Angelica root (*Angelica archangelica*), and also in Roman camomile oil. It melts at 45° and boils at 185° . Tiglic acid has been isolated from croton oil and Roman camomile oil, and is obtained by the fission of many different natural products (saponins, veratrine, etc.). It melts at 64.5° and boils at 198° .

CITRONELIC ACID, $\text{C}_{10}\text{H}_{18}\text{O}_2$, is an oxidation product of citronellal (see p. 170). The compound derived from *d*-citronellal is dextrorotatory. B.p. 152° (18 mm).

UNDECYLENIC ACID, $\text{CH}_2 = \text{CH}(\text{CH}_2)_8\text{COOH}$ is formed by distilling castor oil *in vacuo*. On reduction it gives undecylic acid, $\text{CH}_3(\text{CH}_2)_9\text{COOH}$, and on oxidation, sebacic acid, $\text{HOOC} \cdot (\text{CH}_2)_8 \cdot \text{COOH}$. Its melting point is 24° , and boiling point 213° (100 mm).

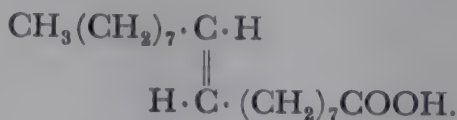
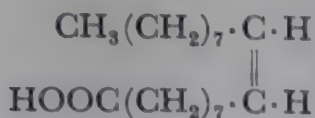
OLEIC ACID and ELAIDIC ACID, $\text{C}_{18}\text{H}_{34}\text{O}_2$. The glycerides of oleic acid are contained in most animal and vegetable fats. Those fats with a low melting point (oils) such as olive oil, almond oil, oil of sesame, coconut oil, linseed oil (with a high content of linoleic and linolenic acids), and lard, are especially rich in oleic acid. The oleic acid is obtained from these by hydrolysis with alkali, the alkali salt is converted into the lead salt, which is separated from the lead salts of the saturated acids by dissolving it in ether.

The constitution of oleic acid is based on the one hand on its reduction to stearic acid, and on the other on its oxidative decomposition to pelargonic and azelaic acids (cf. p. 204).

The pure acid is a colourless, oily liquid, which gradually turns brown in the air and becomes rancid. Its boiling point at 10 mm is 223° , and its melting point, 14° .

If oleic acid is acted upon by small quantities of nitrous acid, nitrogen tetroxide, or nitric acid, or if it is heated with sodium bisulphite, it is converted into

the crystalline, isomeric acid, *elaidic acid*, which has a higher melting point. This has the same structure as oleic acid, and is its geometrical isomeride. The two compounds thus correspond to the formulæ:



Elaidic acid (*trans*-form) melts at 44.2°, and boils at 225° under 10 mm pressure.

Addition of water to both oleic and elaidic acids gives the same hydroxy-stearic acid. Oleic acid is used as a detergent.

RICINOLEIC ACID $\text{CH}_3(\text{CH}_2)_5\text{CHOHCH}_2\text{CH}=\text{CH}(\text{CH}_2)_7\text{COOH}$, is a hydroxy-derivative of oleic acid. Its glyceride is the chief constituent of castor oil. It melts at 4–5°.

ERUCIC ACID and **BRASSIDIC ACID**, $\text{C}_{22}\text{H}_{42}\text{O}_2$. *Erucic acid* occurs as a glyceride in oil of mustard seed, rape oil, haddock liver oil, and some other fats, and is very similar in properties to oleic acid. Thus, it is converted quite easily by nitrous acid into the stereoisomeric brassidic acid. Since oxidation of erucic acid by means of nitric acid leads to the formation of pelargonic acid, $\text{CH}_3(\text{CH}_2)_7\text{COOH}$, and brassylic acid, $\text{HOOC}(\text{CH}_2)_{11}\text{COOH}$, it is concluded that its structure is:



It is the geometrical isomeride of *brassidic acid*. Erucic acid melts at 34°, and boils at 255° (10 mm). Brassidic acid melts at 65° and boils at 256° (10 mm).

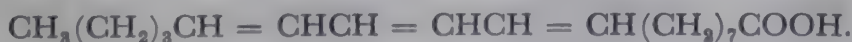
NERVONIC ACID, from the cerebroside of the human brain, has the formula $\text{CH}_3(\text{CH}_2)_7\text{CH}=\text{CH}(\text{CH}_2)_{13}\text{COOH}$. The *cis*-form melts at 39°, the *trans*-form at 61°.

Amongst the unsaturated **carboxylic acids with two or three ethylenic linkages** the following must be mentioned:

GERANIC ACID, $(\text{CH}_3)_2\text{C}=\text{CHCH}_2\text{CH}_2\text{C}(\text{CH}_3)=\text{CHCOOH}$, which is obtainable by the oxidation of citral (see p. 171) or by total synthesis from 2-methylhepten-(2)-one-(6). (See synthesis of citral, p. 171).

LINOLEIC ACID, $\text{CH}_3(\text{CH}_2)_4\text{CH}=\text{CHCH}_2\text{CH}=\text{CH}(\text{CH}_2)_7\text{COOH}$. This compound is a doubly unsaturated stearic acid, and is reduced to the latter by hydriodic acid and phosphorus. The formula, derived from the results of oxidizing the compound, is that given above. Linoleic acid is found as a glyceride, for example, in linseed oil, hemp oil, poppy-seed oil, and also in the lecithin from egg-yolk, in the fat of the whale and sturgeon. It is a light yellow oil, b.p. 229° (16 mm). It is oxidized rapidly in the air, forming a resin. The latter behaviour has earned for it and similar compounds the name "drying acids".

Acids with three double bonds, such as α - and β -elæostearic acid, from Chinese and Japanese wood oil, have particularly well-developed drying properties. The glyceride of α -elæostearic acid is the chief constituent of these oils. Both acids have the structure



They give stearic acid on hydrogenation and on ozonization they form valeric acid and azelaic acid. By irradiation with ultra-violet light the lower melting

α -elæostearic acid (m.p. 47°) is converted into the higher melting β -isomeride (m.p. 67°). They are therefore *cis-trans*-isomerides. Other stereoisomers have been obtained artificially, and from vegetable oils.

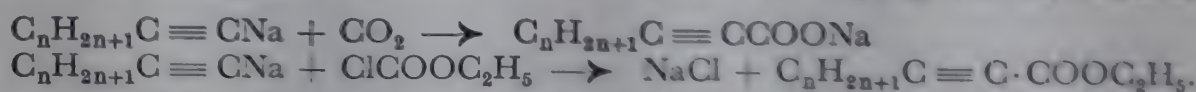
LINOLENIC ACID, which accompanies linoleic acid in linseed oil is ascribed the following formula:



DEHYDROGERANIC ACID, $(\text{CH}_3)_2\text{C} = \text{CHCH} = \text{CHC}(\text{CH}_3) = \text{CHCOOH}$, was discovered in the wood oil of *Callitropsis araucarioides* by Cahn, Penfold, and Simonsen. It can also be obtained by synthesis. Its melting point is 185–186°.

Unsaturated carboxylic acids with triple bonds

For those acetylenic carboxylic acids in which the triple bond is next to the carboxyl group, a good synthesis is to allow the sodium salts of the corresponding acetylenic hydrocarbons to react with carbon dioxide or chlorocarbonic ester. In the latter case the ester of the acid is obtained (Lagermark, Moureu):



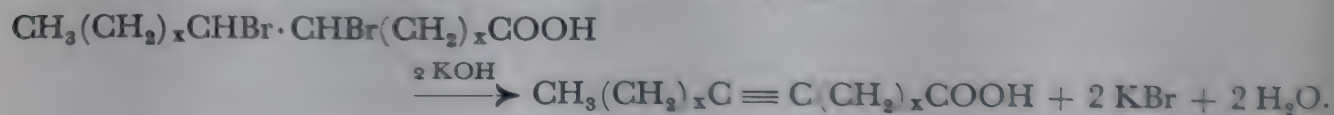
The simplest compound of this class is PROPIOLIC ACID, $\text{HC} \equiv \text{C} \cdot \text{COOH}$, after which the whole series is named the propiolic acid series. It is a pungent smelling liquid, b.p. 83° (50 mm), m.p. 9°. The hydrogen atom of the acetylenic radical, in addition to that of the carboxyl group can be replaced by a metal.

Many of the higher homologues of propiolic acid are known. TETROLIC ACID (b.p. 203°), $\text{CH}_3\text{C} \equiv \text{C} \cdot \text{COOH}$, and HEPTYNECARBOXYLIC ACID



the methyl ester of which is used in artificial violet leaves perfume, may be mentioned.

Carboxylic acids in which the triple bond is further removed from the carboxyl group, may be obtained from certain dibromo-derivatives of the fatty acids by elimination of hydrogen bromide by means of alkalis:



Thus, dibromostearic acid can be made by the addition of bromine to oleic acid. Boiling this with alcoholic potash gives STEAROLIC ACID, of which the constitution is arrived at by oxidative degradation:



Esters of the carboxylic acids

METHODS OF FORMATION. The esters of the carboxylic acids are made in similar ways to other esters (p. 73). The process most frequently used is the action of the concentrated alcohol on the concentrated carboxylic acid. The mixture of the two substances is heated after addition of some concentrated sulphuric acid, or after saturation with hydrogen chloride, since the equilibrium

is attained only very slowly in the cold. Often a fairly small amount of hydrogen chloride (3-5 per cent) is sufficient to aid the esterification:



Moreover, the rate of formation of the ester depends to a great extent on the nature of the carboxylic acid and of the alcohol. Primary alcohols react more quickly than secondary, and secondary than tertiary. Similar gradations in reaction rates are found with the carboxylic acids, according as they contain the carboxyl group attached to a primary, secondary, or tertiary carbon atom (Menschutkin). The first members, methyl alcohol and formic acid react the most readily.

Another method frequently employed for the preparation of esters of the carboxylic acids is the interaction of salts of the carboxylic acids with alkylating agents (alkyl halides, dialkyl sulphates). The yields are usually very good:



Also the interaction of acid chlorides and alcohols proceeds smoothly, and is suitable for the preparation of the esters of the carboxylic acids:

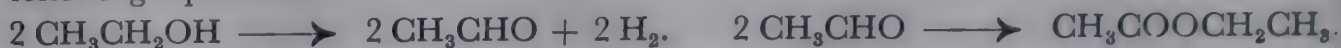


		Natural Occurrence	Constituent of artificial	b.p.
HCOOC ₂ H ₅	Ethyl formate		Rum, raspberry, red-currant, mirabelle, peach essences.	55°
CH ₃ COOC ₂ H ₅	Ethyl acetate		Apple, pear, strawberry, raspberry, red-currant, mirabelle, peach essences.	77°
CH ₃ COOC ₅ H ₁₁	<i>Isoamyl</i> acetate		Pine-apple, pear, raspberry essences	142°
CH ₃ COOC ₈ H ₁₇	Octyl acetate	In Heracleum oil		210°
C ₃ H ₇ COOC ₂ H ₅	Ethyl butyrate		Pine-apple, banana, strawberry, raspberry, red-currant, mirabelle essences.	120°
C ₃ H ₇ COOC ₅ H ₁₁	<i>Isoamyl</i> butyrate		Pine-apple, banana, strawberry, raspberry, peach essences	178°
C ₃ H ₇ COOC ₆ H ₁₃	Hexyl butyrate	In Heracleum oil		205°
C ₃ H ₇ COOC ₈ H ₁₇	Octyl butyrate	In the oil of the fruit of <i>Pastinaca sativa</i>		244°
C ₄ H ₉ COOC ₂ H ₅	Ethyl <i>isovalerate</i>		Raspberry, peach essences	134°
C ₄ H ₉ COOC ₅ H ₁₁	<i>Isoamyl isovalerate</i>	In bananas	Apple, pine-apple, peach essences	194°
C ₈ H ₁₇ COOC ₅ H ₁₁	Octyl ester of caproic acid	In Heracleum oil		275°
C ₈ H ₁₇ COOC ₂ H ₅	Ethyl ester of oenanthic acid		Red-currant, raspberry essences	187°
C ₈ H ₁₇ COOC ₃ H ₇	Ethyl ester of pelargonic acid		Quince essence	227°

In certain cases special methods can be useful for the preparation of these esters. Thus, alkyl formates are produced when carbon monoxide and liquid alcohols react with each other at high pressures and in the presence of a catalyst (e.g. sodium):



Ethyl acetate is formed when ethyl alcohol is passed over special contact catalysts (e.g. a mixed catalyst of copper and cerium). The process is probably represented by the following equations:



PROPERTIES. The esters of the carboxylic acids are neutral liquids which are split into their components (hydrolysed or "saponified") slowly in the presence of moisture, and more rapidly by bases and acids. The hydroxyl ions of the base and the hydrogen ions of the acid catalyse the hydrolysis, the hydroxyl ion being more effective than the hydrogen ion. Technically, hydrolysis is usually carried out by alkalis, but it sometimes happens that the substances are affected in some other way by alkalis, in which case acid hydrolysis is used.

Whilst the hydrolysis of esters with water and mineral acids gives the alcohol and the free carboxylic acid, if alkali is used the salt of the acid is obtained. The alkali is thus used up in the reaction:



If sufficient alkali is used to neutralize all the carboxylic acid produced, the hydrolysis of the ester proceeds to completion.

For the replacement of the alcohol radical of an ester by another alkyl radical (transesterification) see p. 87.

It sometimes happens that certain esters, on heating with alcohols, are hydrolysed, *ethers* being formed in the process (alcoholysis). This course of the reaction is of importance in understanding the reaction-mechanism of the hydrolysis of esters, as it proves that the fission takes place at the linkage between alkyl and oxygen, and not between acyl and oxygen (S.G. Cohen, A. Schneider):



The simpler esters of the carboxylic acids are liquids and often possess a pleasant smell. The higher esters are oily, fatty, or wax-like in consistency.

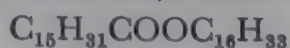
Three large groups of esters of the carboxylic acids, which are of great importance as natural products and in industry, may be recognized:

- (a) the *fruit essences*, esters of lower and middle carboxylic acids with lower and middle alcohols,
- (b) the *fats*, esters of glycerol with higher and middle fatty acids,
- (c) the *waxes*, esters of the higher monohydric alcohols with the higher carboxylic acids.

Fruit essences. These esters are characterized by their pleasant odours. Some of them are constituents of essential oils, many of them are obtained synthetically, and are used in perfuming fruit juices, mineral waters, etc. Ethyl acetate, $\text{CH}_3\text{COOC}_2\text{H}_5$, is also used in medicine as a stimulant.

Waxes. The various kinds of waxes consist predominantly of esters of the higher monobasic carboxylic acids with the higher monohydric (more seldom dihydric) alcohols. In addition they always contain free acids, free alcohols, and often hydrocarbons.

Thus, the palmitic ester of myricyl alcohol, $\text{CH}_3(\text{CH}_2)_{14}\text{COOC}_{31}\text{H}_{63}$, is the chief constituent of *beeswax*, which also contains cerotic acid (10–14 per cent) and hydrocarbons (12–17 per cent). The cetyl ester of palmitic acid,



predominates in *spermaceti*, the solid constituent of sperm oil which occupies the head of the sperm whale. *Chinese insect wax*, the excretion of a cochineal insect, consists chiefly of the ceryl ester of cerotic acid,



Carnauba wax, the wax of a Brazilian fan-palm consists of the myricyl ester of cerotic acid, $\text{C}_{25}\text{H}_{51}\text{COOC}_{31}\text{H}_{63}$, the free acids (Carnauba acid, cerotic acid), higher alcohols, and a hydrocarbon. The vegetable waxes are very widely spread, but have been little investigated. Candelilla wax (obtained from a *Euphorbiacea*) is an article of commerce.

Wool wax, the neutral portion of wool fat, has a somewhat different composition, for it contains the complex alcohol cholesterol belonging to the carbocyclic compounds, in addition to higher fatty acids and hydrocarbons.

The waxes are of considerable practical importance in the manufacture of candles, wax works, gramophone records, and boot-polishes, in lithography and electro-plating, and as ingredients of soaps, plasters, pomades, etc.

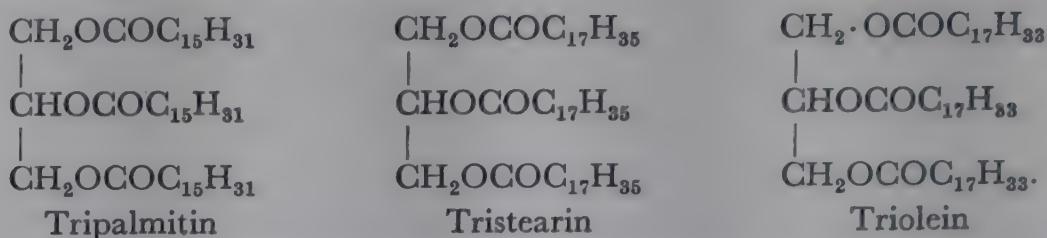
Fats and oils.¹ The fats and oils are entirely glycerides, i.e. esters of the trihydric alcohol glycerol with higher and middle fatty acids. In the animal and vegetable kingdoms they are exceedingly widely spread. In industry, however, the fats of only a few animals, and relatively few plants rich in oil are used. Amongst the fats of animal origin which are most used technically are butter, beef fat, mutton fat, and lard, and of plant oils, olive oil, rape oil, almond oil, peanut oil, palm oil, and some of higher consistency, such as cocoa butter, shea butter, laurel fat, and nutmeg butter.

In addition to these fats and oils which do not markedly change their consistency on standing in air, there are the so-called *drying oils*, which, under the influence of atmospheric oxygen gradually resinify and become solid. Linseed oil, hemp oil, poppy-seed oil, and wood oil belong to this class. They are much used for the manufacture of varnishes.

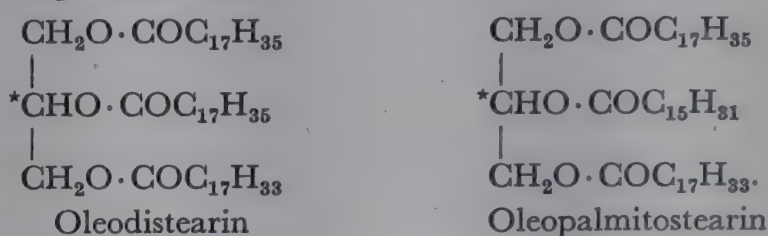
The melting point, and therefore the consistency of a fat depends on the nature of the acid which takes part in its structure. Hard fats, i.e. those with high melting points, are chiefly *glycerides of palmitic and stearic acids*, whilst the lower melting oils are composed largely of *glycerides of oleic acid*. The phenomenon of a double melting point is characteristic of many glycerides, i.e. they melt at a certain temperature, but on further heating become solid again, and liquefy a second time at a higher temperature. Thus, tripalmitin first melts at 43°, and

¹ Cf. G. D. ELSDON, *The Chemistry and Examination of Edible Oils and Fats, Their Substitutes and Adulterants*, London, (1926). — AD. GRÜN and W. HALDEN, *Analyse der Fette und Wachse*, Vols. I and II, Berlin, (1925 and 1929). — H. HELLER, *Ubbelohdes Handb. d. Chemie und Technologie der Öle und Fette*, Leipzig, (1929). — D. HOLDE, *Kohlenwasserstofföle und Fette*. 7th ed., Berlin, (1933). — H. SCHÖNFELD, *Chemie und Technologie der Fette and Öle*. (5 vols.). Vol. I (ed. by Arentz), Vienna, (1936). — T. P. HILDITCH, *The chemical constitution of natural fats* London, (1940). — E. GILDEMEISTER and F. HOFFMANN, Transl. by E. KREMERS, *The Volatile Oils*, London, (1940). — W. R. BLOOR, *Biochemistry of the Fatty Acids and Their Compounds, the Lipids*, New York, (1943). — G. S. JAMIESON, *Vegetable Fats and Oils*, 2nd ed., London, (1944). — H. G. KIRSCHENBAUER, *Fats and Oils*, New York, (1945).

for a second time at 65° . Tristearin melts at 55° and 72° . Triolein, however, melts at a much lower temperature and exists in 3 polymorphous forms melting at -32° , -13° , and -5.5° . A satisfactory theoretical explanation of this phenomenon has not yet been arrived at.



All natural fats are mixtures of various glycerides, and are made up not only of symmetrical compounds, i.e. glycerides of which the three fatty acid radicals are all the same, but also of mixed compounds which contain two or three different acyl radicals in the molecule. Such a compound is oleodistearin, and another is oleopalmitostearin:



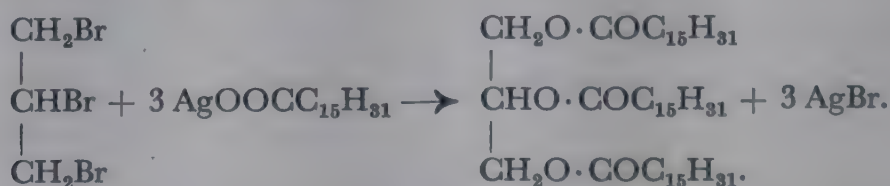
The oleodistearin, isolated from different fats, proved to be identical with β -oleodistearin.

For the unsymmetrical forms, theory predicts asymmetrical structure and therefore optical activity. However, up to the present no natural fats have been shown to possess optical activity, except those which, like chaulmoogra oil, contain an asymmetric acid. Perhaps they racemize very easily, and thus become inactive either in the general sense, or by wandering of the acyl groups. Acyl group wandering in the glycerides can easily occur, and has been repeatedly observed.

It is possible, however, to synthesize fats which will rotate the plane of polarization of light (Abderhalden, M. Bergmann).

Very recently, B. Suzuki claims to have shown that freshly obtained natural fats and oils may be optically active. This observation needs further confirmation.

Symmetrical glycerides can be synthesized comparatively easily by treating tribromohydrin with the silver salts of the fatty acids:



On the other hand, the synthesis of a definite *mixed* glyceride presents some difficulty, caused particularly by the fact that the acyl radicals, under certain circumstances, can wander from one hydroxyl of the glycerol to another. By choosing suitable methods it is possible to overcome these difficulties, so that a number of mixed glycerides of definite structure is now known (A. Grün, Bergmann).

Although palmitic, stearic, and oleic acids are by far the most common acids

present in natural fats and oils, there are also natural glycerides of other carboxylic acids. *Butter* contains *tributyrin*, the glyceryl ester of butyric acid, together with the glycerides of caproic, caprylic, and capric acids. The glyceride of lauric acid is contained in laurel oil and glycerides of myristic acid in nutmeg butter, and coconut fat. Arachidic acid is found as a glyceride in peanut oil, and the glyceride of behenic acid in rape oil, etc. The unsaturated erucic acid (see p. 209) has already been mentioned as a constituent of certain fats. The glyceride of linoleic acid is found in linseed oil and other drying oils¹, and the glyceride of ricinoleic acid is found in castor oil. Fish liver oils contain the glycerides of even more strongly unsaturated acids, such as *therapinic acid*, $C_{16}H_{25}COOH$, and a hexaethylenic acid with 22 C-atoms from which probably clupanodonic acid, $C_{21}H_{33}COOH$, is produced on distillation. *Arachidonic acid*, isolated from phosphatides, is also strongly unsaturated; its constitution corresponds to 5:8:11:14-eicosanetetraenoic acid,



The unsaturated fats may be converted by hydrogenation into more, or completely, saturated fats. This process, known as "*hardening of fats*" and first introduced by Normann, has very great technical importance, since in the manufacture of soap, stearin, and margarine, fats with higher melting points are needed, but these (they are usually animals oils) are higher in price than many vegetable oils. A great industry has therefore grown up in recent years for the conversion of the less useful plant fats and fish oils into solid fats by hydrogenation. The hydrogenation is carried out with hydrogen under slight pressure, nickel, in a finely divided form distributed throughout the oil, being used as a catalyst. By suitable agitation or spraying devices a good contact between the fat and the hydrogen is ensured.

According to new researches, especially those of H. J. Waterman, in the hardening of fats not only does hydrogenation take place, but also "*elaidinization*", i.e. the isomerization of oleic acid into elaidic acid and a consequent increase in the melting point of the fat. Hardening of fats can also be accomplished by heating with nickel alone or better with SO_2 at 110–115°; here also "*elaidinization*" occurs. On heating with SO_2 to a still higher temperature a rearrangement of linoleic acid into acids with conjugated double bonds also takes place. In this case, the melting point and at the same time the oxidizability and polymerizability increase, i.e. it becomes a "*drying oil*".

The *saponification* (or hydrolysis) of fats — a process carried out technically on a large scale — can be brought about by water alone, or by acids or alkalis. In the first case, the fat is treated with superheated water in autoclaves at about 170° (6–8 atmospheres pressure). Zinc oxide or lime is used as a catalyst. The hydrolysis will take place at much lower temperatures (below 40°) if fat-hydrolysing enzymes, lipases, are added to an emulsion of the fat in water. Enzymes which hydrolyse fats are found in the alimentary canal of most animals and man. They are secreted from the pancreas and serve to break down the oils and fats taken in food. Lipases are also contained in plants. That occurring abundantly in the seeds of *Ricinus*, is used, according to a process worked out by Connstein, to decompose fats into glycerol and fatty acids on a technical scale. The process is carried out in very weakly acid solution, in which the *Ricinus* lipase is most effective.

¹ R. S. MORREL and H. R. WOOD, *The Chemistry of Drying Oils*, London, (1925).

In recent times the hydrolysis of fats by means of a mixture of sulphonic acids, obtained by sulphonation of a mixture of oleic acid (or castor oil) and naphthalene (or benzene), has attained some technical importance. If it is added to the water in small quantity fats are very rapidly hydrolysed even at 100° by this reagent (Twitchell process).

Formerly fats were often saponified by treatment with concentrated sulphuric acid at 100–120°. The process has, however, certain disadvantages. The fatty acids are dark-coloured, and the glycerol is partly decomposed. On the other hand there are certain advantages. The oleic acid (by addition of sulphuric acid, and subsequent decomposition of the ester by water) is converted into hydroxystearic acid, which, on distillation gives solid *isoo*leic acid. The yield of solid acids is thus increased. Often nowadays the fats which have been to a large extent saponified by the autoclave or Twitchell process are separated from the water containing glycerol, and the remaining unhydrolysed fats present in the fatty acids obtained, are then completely saponified by means of a little concentrated sulphuric acid.

The hydrolysis of fats by caustic soda or caustic potash is usually employed when *soaps*¹ are to be made. Soaps are the alkali salts of the higher fatty acids. The raw materials technically used for their manufacture are animal fats (tallow), palm oil, coconut oil, cotton-seed oil, etc. If these are heated with sodium hydroxide solution, a liquid which contains the glycerol and salts of the fatty acids is formed. Common salt is then added to the liquid whilst it is still hot, when the sodium soaps are salted out.

Sodium soaps, after solidifying, possess a solid and hard consistency; they are called *hard soaps*. The *soft soaps* are chiefly potassium soaps. They are obtained by the hydrolysis of the less valuable oils (linseed oil, fish oils, hemp oil) by means of caustic potash, but the potassium salts of the fatty acids are not separated — a process which would be too expensive — so that potassium soaps still contain large quantities of water and glycerol. Sodium soaps are also sometimes manufactured without troubling to separate the alkali salts from the glycerol and water. The whole mass, on cooling becomes semi-solid.

In more recent times the tendency has been to hydrolyse fats for soap-manufacture not by alkali, but by the autoclave or Twitchell process, thus obtaining the free fatty acids, and then converting these into soaps by neutralization with sodium or potassium hydroxide.

All soaps, being the alkali salts of very weak acids, are partially hydrolysed in aqueous solution to the free fatty acids and alkali hydroxides, and their solutions therefore react alkaline:



The free fatty acid remains to a large extent emulsified in the water if warm, and on cooling combines with undissociated soap molecules giving an acid salt, a molecular compound which is very difficultly soluble, and is therefore precipitated: $\text{C}_{17}\text{H}_{35}\text{COOH}, \text{C}_{17}\text{H}_{35}\text{COONa}$.

These soap solutions lather on shaking with air, air-bubbles being enclosed in a thin film of the liquid. The lather is not formed, however, if so-called hard water, containing calcium and magnesium salts is used to prepare the soap solution, since in this case the fatty acids are precipitated as insoluble calcium and magnesium salts. Hard water is unsuitable for washing purposes. It uses up the soap, which it precipitates as insoluble salts.

The detergent action of a soap solution depends only to a slight extent on its

¹ J. H. WIGNER, *Soap Manufacture; the Chemical Processes*, London, (1940).

alkaline reaction. Colloidal processes play the chief part. The dirt and grease particles on the skin are emulsified by the colloiddally dispersed fatty acids and soap, and are removed by adsorption. The scouring effect of the lather may also exert some influence.

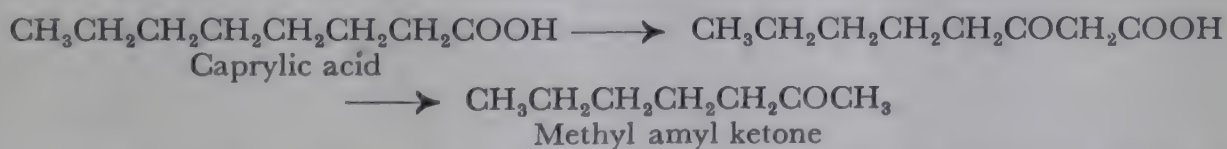
For the manufacture of stearin candles, the solid fatty acids, particularly palmitic and stearic acids (stearin) are used. In order to separate this mixture from oleic acid, the mixture of fatty acids formed by the saponification of the fats, is expressed at low temperatures. The oleic acid is squeezed out. Since the process of hardening of fats has been used technically, it is possible to obtain solid fatty acids suitable for making candles also from strongly unsaturated oils. For white candles the crude stearin must be purified by distillation in steam. Finally it is moulded into stearin candles, sometimes with the addition of paraffin wax.

In addition to the alkali salts, the lead salts of the fatty acids have some practical use. They can be obtained directly from the fats by hydrolysis with an aqueous suspension of lead oxide, and are used in medicine as plasters (lead plaster). They are amorphous and can be kneaded.

The fats, in addition to proteins and carbohydrates form the principal portion of our food, and that of very many animals. They are broken down into glycerol and fatty acids in the intestines by the fat-hydrolysing enzymes, the lipases, and within and outside the intestinal walls are re-formed from the two components. Furthermore the animal organism is capable of converting carbohydrates into fats, and this reaction is the most important source of fats in plants. In the animal body and in plants (especially seeds) fats are stored as reserve food material.

It has been known for a long time that most fats become *rancid* on keeping, especially if exposed to light and air. Whilst it was formerly supposed that the rancid smell was due to traces of fatty acids formed by decomposition, more recent work of Fierz and Stärkle, Haller and Tschirch, shows that various types of decomposition take place. The rancidity can be produced without the action of bacteria or fungi simply by light and water in the case of the unsaturated fats. The unsaturated fatty acids break down into aldehydes and acids (perhaps ricinoleic acid also does this). Saturated fatty acids do not change under these conditions.

It is also possible, however, for fats to become rancid by the action of bacteria and moulds. This decomposition is also suffered by those fats containing saturated acids. The moulds attack the saturated carboxylic acids according to the principle of β -oxidation, though, however, β -hydroxy-acids which are the normal intermediate products in cases of β -oxidation (see p. 197) are probably not formed here, as moulds are unable to convert them into ketones.



The process has been accurately followed with the salts of the pure fatty acids. These are decomposed by *Penicillium glaucum* into ketones, caprylic acid giving methyl amyl ketone, capric acid giving methyl heptyl ketone, lauric acid giving methyl nonyl ketone, myristic acid giving methyl undecyl ketone, etc. Carboxylic acids with odd numbers of carbon atoms behave in an analogous manner, heptylic acid giving methyl butyl ketone, and nonylic acid giving methyl hexyl ketone, for example.

The fats themselves are first hydrolysed by the micro-organisms, e.g. *Penicillium glaucum* or *Aspergillus niger*, and then undergo decomposition to ketones

in the same way. From rancid cocoa-butter methyl amyl ketone, methyl heptyl ketone, methyl nonyl ketone, and methyl undecyl ketone were isolated, having been derived from caprylic, capric, lauric, and myristic acids, the glycerides of which form the chief constituents of coconut fat. The ketones smell unpleasant, and are the cause of the rancid smell.

Thus the decomposition of fats by moulds furnishes one of the best examples of the importance of β -oxidation in biology.

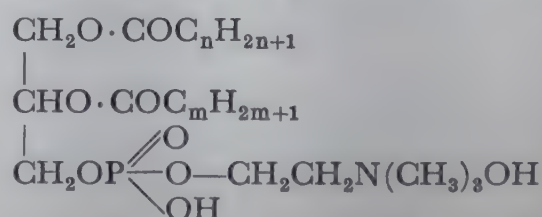
Phosphatides.¹ The *phosphatides* are fat-like substances which, however, contain phosphorus and a basic component [choline, colamine (ethanolamine)]. They are very widely spread in the animal and vegetable kingdoms. Since they are exceedingly important compounds physiologically, probably no living organism is quite devoid of them. They are particularly abundant in egg-yolk and in the brain, but can also be easily extracted from many plant seeds.

According to the latest discoveries it is convenient to divide the phosphatides into *ester phosphatides*, the phosphatides of classical physiological chemistry, and *acetal phosphatides*, discovered by Feulgen. In the former, higher fatty acids participate in building up the molecule, and in the latter, higher aldehydes.

A. ESTER PHOSPHATIDES.

The best known ester phosphatide is **lecithin**, which is usually isolated from egg-yolk, and more seldom from brains. It is easily soluble in both alcohol and ether, and is distinguished in this respect from *kephalin* (see below), a related phosphatide which usually accompanies lecithin, which is difficultly soluble in alcohol.

Lecithin, or better the lecithins, since there is a whole group of related substances, are decomposed by hydrolysis into 2 molecules of a fatty acid (palmitic, stearic, or oleic, perhaps also linoleic acid, and others), 1 molecule of glycerol, 1 molecule of phosphoric acid, and 1 molecule of choline $\text{HOCH}_2\text{CH}_2\text{N}(\text{CH}_3)_3\text{OH}$. The identification of these fission products as well as the results of the partial hydrolysis of lecithin has led Strecker to propose the formula



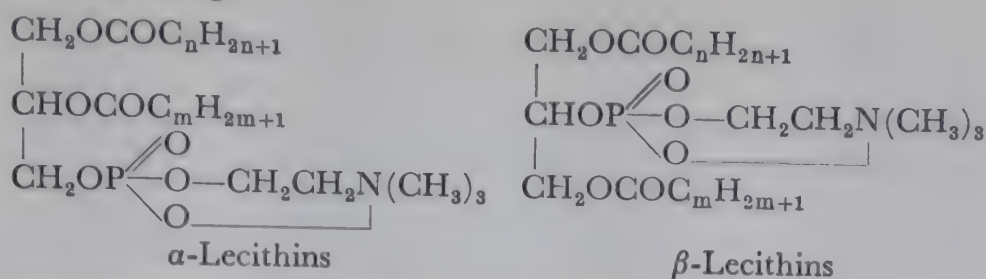
for lecithin. In this formula, the two fatty acid radicals can be varied, making possible a large number of isomeric, homologous, and analogous lecithins. It was shown later that crude lecithin preparations lacked uniformity also in another respect, for they are derived in part from α -glycerophosphoric acid and in part from β -glycerophosphoric acid:



the first of which could be obtained from lecithin in an optically active form

¹ HUGH and IDA S. MACLEAN, *Lecithin and allied substances. The Lipids*, 2nd ed., London, (1927). — HANS THIERFELDER and E. KLENK, *Die Chemie der Cerebroside und Phosphatide*, Berlin, (1930). — HENRY B. BULL, *The biochemistry of the lipids*, New York, (1937).

(lævorotatory, L-configuration), the second, being symmetrical, was obviously inactive. Lecithin is therefore a mixture of α -lecithins and β -lecithins, the latter strongly predominating:



(This formulation takes into account that the link between the phosphate and choline radicals is probably a betaine link.)

Various lecithins have been prepared artificially by A. Grün.

The lecithins are very hygroscopic, and rapidly alter in the air. They are usually amorphous, but crystallize from ether at low temperatures. They are used in medicine as tonics.

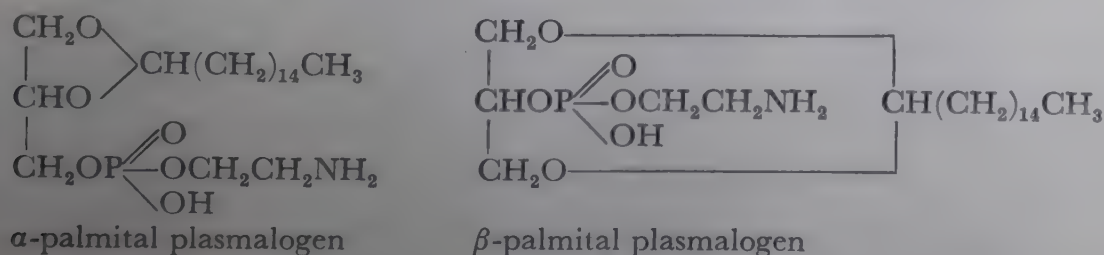
KEPHALIN belongs to the same group of compounds as the lecithins, but instead of having choline united to the glyceryl-phosphate radical it has ethanolamine (*colamine*). Moreover it contains an amino-acid (serine). Use is made of its low solubility in alcohol to separate it from lecithin.

In addition to lecithin and kephalin, many other phosphatides have been described in the literature, some of which are assumed to contain nitrogen and phosphorus not in the ratio 1:1, but 1:2, or 2:1, etc. Their homogeneity, however, is even less certain than that of the lecithin and kephalin preparations. Compounds related to the phosphatides, such as *sphingomyelin*, *protagon*, *cerebron*, and similar substances, have been isolated from the brain.

B. ACETAL PHOSPHATIDES.

The *acetal phosphatides*, recently discovered by Feulgen, are always mixed (in quantities up to 12 per cent) with the ester phosphatides. They are particularly abundant in the phosphatide fraction from muscle and brain. It is not easy to separate them from the ester phosphatides; the separation is best accomplished after the alkaline hydrolysis of the accompanying ester phosphatides. For these compounds the name of "plasmalogen" has also been introduced.

The plasmalogens differ from the ester phosphatides in that in the former instead of fatty acid residues, a higher aldehyde (palmitic aldehyde, stearic aldehyde) binds the two free hydroxyls of the glycerophosphoric colamine ester as in acetals. Thus, the two structurally isomeric palmital plasmalogens have the following formulæ:



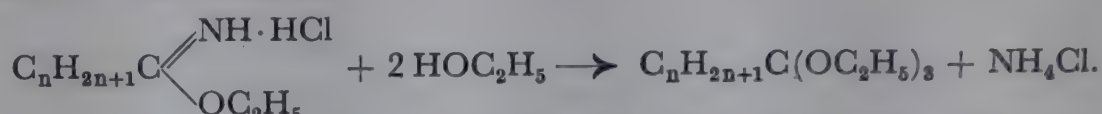
By means of careful acid hydrolysis, e.g. with HgCl_2 , these compounds can be split up into the colamine ester of α - or β -glycerophosphoric acid, respectively, and aldehydes. The mixture of higher aldehydes thus formed has been called "plasmal". It contains palmitic aldehyde, stearic aldehyde, and other aldehydes

that have not yet been further investigated. Like other acetals, the acetal phosphatides are much more stable towards alkalis than towards acids.

Esters of the orthocarboxylic acids¹

Although the orthocarboxylic acids, $R \cdot C \begin{smallmatrix} \nearrow OH \\ \searrow OH \end{smallmatrix}$, do not exist in the free state,

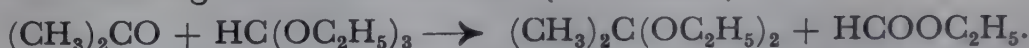
their esters can be obtained from the hydrochlorides of the imido-ethers (see p. 225) by interaction with alcohol:



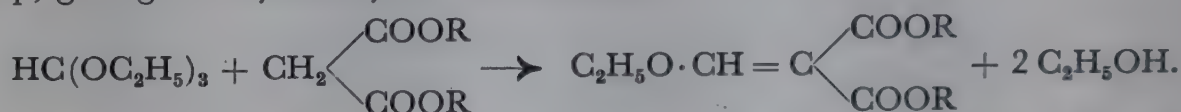
They are also produced from chloroform and other trihalogen compounds by the action of sodium alcoholates:



In preparative chemistry the ortho-esters of formic acid are used in the preparation of the acetals of aldehydes, and more especially of ketones. This is the easiest method for obtaining the ketone acetals (L. Claisen):



They also condense easily with compounds containing a reactive methylene group, giving alkoxyethylene derivatives:

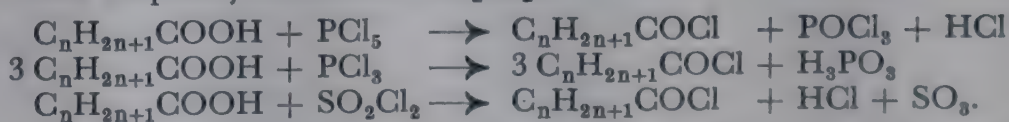


The esters of the orthocarboxylic acids are liquids which can be distilled without decomposition, and which possess an ester-like smell. They are very stable towards alkalis, but are readily hydrolysed by acids, the cleavage leading either to the ordinary esters, or the free carboxylic acids, according to the conditions.



Acid halides of the carboxylic acids

Of the *acid halides of the carboxylic acids* the *chlorides* are the most common. They are prepared by the action of phosphorus pentachloride, phosphorus trichloride, or thionyl chloride on the free acids. Technically they are also prepared from sulphuryl chloride SO_2Cl_2 :



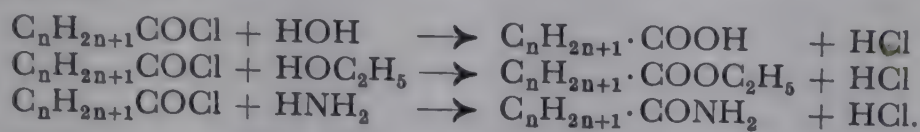
The *acid bromides* can be synthesized in a similar way using phosphorus bromides. The *acid iodides* can be obtained from the anhydrides or salts of the carboxylic acids by the action of phosphorus iodide, or by the action of calcium iodide on the acid chlorides. Acid fluorides are obtained from the acid chlorides and potassium fluoride.

Alkyl halides will add on to CO at 700–900° in the presence of an indifferent metal (e.g. copper), if the time for which the gases are in contact with the metal does not exceed 0.3 sec.

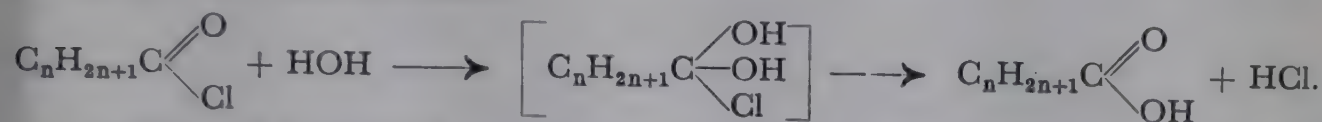
¹ H. W. POST, *The Chemistry of Aliphatic Ortho esters*, New York, (1943).

The lower acid chlorides are mobile liquids with a pungent smell. They can be distilled, and fume in air. The last property depends on the fact that they are easily hydrolysed by moisture to give hydrogen chloride. The higher acid chlorides are crystalline solids.

The halogen atom of the acid halides is characterized by great mobility. It is easily replaced by the most diverse groups (OH, OC₂H₅, NH₂, NHOH, NHNH₂, N₃, and others). This is why the acyl halides are so important. They serve for the introduction of the acyl radical into other substances. With water they give carboxylic acids, with alcohols esters, with amines acid amides, with hydroxylamine hydroxamic acids, etc.:



It is probable, however, that all these reactions take place in two stages, the primary process being not the substitution of the halogen, but the addition of the alcohol, water, and so on, across the carbonyl double bond of the acid chloride, which under the influence of the neighbouring halogen is rendered specially active (A. Werner). In the second phase the halogen hydride is eliminated:



This view is supported by many observations. Thus, the acid fluorides, RCOF, react much more rapidly with the Grignard reagent than acid chlorides and acid bromides. Since fluorine is, in general, much more strongly attached to the carbon than is chlorine or bromine, it follows that the reaction cannot be a double decomposition, but begins with an addition of RMgX to the CO double bond.

Use is made of the acid chlorides in the determination of the constitution of organic compounds, to find out the number of hydroxyl or primary or secondary amino groups present, since each can take up an acyl group.

CH ₃ COCl	acetyl chloride, b.p. 51°
C ₂ H ₅ COCl	propionyl chloride, b.p. 78°
C ₃ H ₇ COCl	<i>n</i> -butyryl chloride, b.p. 101°
C ₄ H ₉ COCl	<i>n</i> -valeryl chloride, b.p. 128°
C ₅ H ₁₁ COCl	<i>n</i> -caproyl chloride, b.p. 152°
C ₆ H ₁₃ COCl	oenanthyl chloride, b.p. 175°
C ₇ H ₁₅ COCl	caprylyl chloride, b.p. 195°
C ₈ H ₁₇ COCl	pelargonyl chloride, b.p. 220°
C ₉ H ₁₉ COCl	capryl chloride, b.p. 114° (15 mm)
C ₁₁ H ₂₃ COCl	lauryl chloride, b.p. 142° (15 mm), m.p. —17°
C ₁₃ H ₂₇ COCl	myristyl chloride, b.p. 168° (15 mm), m.p. —1°
C ₁₅ H ₃₁ COCl	palmityl chloride, b.p. 192° (15 mm), m.p. 12°
C ₁₇ H ₃₅ COCl	stearyl chloride, b.p. 215° (15 mm), m.p. 23°.

Formyl chloride is unknown in the free state, but double compounds of it and aluminium chloride are known, made by the action of carbon monoxide and hydrogen chloride on aluminium chloride under pressure. Formyl fluoride is more stable, and has been isolated in a state of purity.

Acid anhydrides, (C_nH_{2n+1}CO)₂O

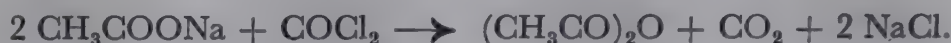
Anhydrides of the carboxylic acids, especially those of the higher members, may be conveniently obtained from the anhydrous acids by the action of a dehydrating agent. In many cases acetic anhydride or acetyl chloride are suitable, in others phosphorus pentoxide, the acid being distilled with them:



The synthesis of acid anhydrides by the interaction of acid chlorides and salts of the fatty acids is of general application:

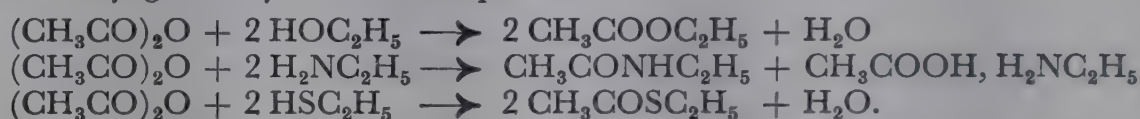


If the salt and the chloride are not derived from the same acid the process gives mixed acid anhydrides. Often it is unnecessary to work with the pure acid chloride. It is sufficient to act upon the fatty acid salt with enough phosphorus oxychloride, carbonyl chloride, or sulphuryl chloride, to convert half of it into acid chloride. The latter then reacts with the other half of the salt to give the anhydride:



With the exception of the anhydride of formic acid, which does not appear to exist, the anhydrides of all the fatty acids are easily obtainable. The lower members are mobile liquids with a pungent smell; the higher members are odourless and solid.

In syntheses use is very often made of acid anhydrides, especially the simpler ones, for "acylation". Like the acid chlorides, the anhydrides are useful substances for introducing the carboxylic acid radical, $\text{C}_n\text{H}_{2n+1}\text{CO}$ into other compounds. With alcohols they react to give esters, with amines they give amides, with mercaptans they give acylated mercaptans:



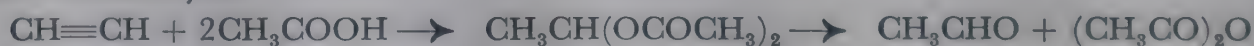
The reactivity of the anhydrides depends on their molecular weight. The lower ones react more vigorously than the higher. Whilst acetic anhydride is almost instantaneously converted into acetic acid by warm water, the higher anhydrides require long heating of the aqueous suspension. Their smaller reaction rate is probably due to their insolubility, and that of the acids produced.

$(\text{CH}_3\text{CO})_2\text{O}$	acetic anhydride, b.p. 136°
$(\text{C}_2\text{H}_5\text{CO})_2\text{O}$	propionic anhydride, b.p. 168°
$(\text{C}_3\text{H}_7\text{CO})_2\text{O}$	butyric anhydride, b.p. 192°
$(\text{C}_4\text{H}_9\text{CO})_2\text{O}$	isovaleric anhydride, b.p. 215°
$(\text{C}_5\text{H}_{11}\text{CO})_2\text{O}$	caproic anhydride, b.p. 241°
$(\text{C}_6\text{H}_{13}\text{CO})_2\text{O}$	oenanthic anhydride, b.p. 258°
$(\text{C}_{15}\text{H}_{31}\text{CO})_2\text{O}$	palmitic anhydride, m.p. 64°
$(\text{C}_{17}\text{H}_{35}\text{CO})_2\text{O}$	stearic anhydride, m.p. 72°.

Acetic anhydride, which is of importance for technical purposes, is now manufactured by the action of ketene on acetic acid:



or from acetylene which, in the presence of mercury salts, adds on acetic acid yielding ethylidene diacetate. The latter on distillation breaks down smoothly into acetic anhydride and acetaldehyde:



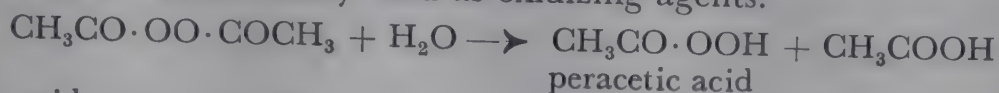
Diacyl peroxides and Peracids.

When anhydrides of aliphatic carboxylic acids (acetic, butyric acid anhydride, etc.) act on barium peroxide or hydrogen peroxide, e.g. in ether solution, diacyl peroxides are formed:



Diacyl peroxides are oxidizing agents and as such are used in preparative organic chemistry. — Diacetyl peroxide melts at 27°; it is explosive and is decomposed on ultra-violet irradiation into CO₂, ethane, and small quantities of methane, ethylene, etc.

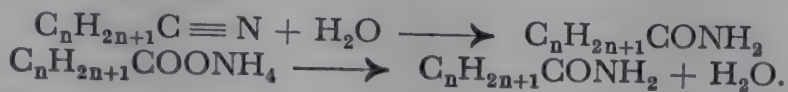
Water hydrolyses the diacyl peroxides to *per-acids*. These also have oxidizing properties and are occasionally used as oxidizing agents.



Perbutyric acid: m.p. —10.5°
(preparation 95 % pure)

Acid amides, C_nH_{2n+1}CONH₂.

The most important methods of formation of the acid amides have already been mentioned, viz. the partial hydrolysis of the nitriles (see p. 188) with hydrogen peroxide or mineral acids, and the partial dehydration of the ammonium salts of the fatty acids by heat:



Also, it has been mentioned that the acid chlorides and anhydrides give acid amides when treated with ammonia and its derivatives.

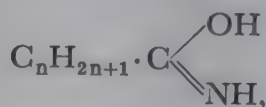
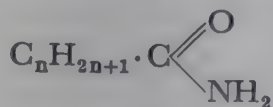
Finally, a convenient method of preparing them is from the esters of the carboxylic acids. They are allowed to stand for some time at room temperature with solutions of ammonia or amines, when the following reaction often takes place smoothly:



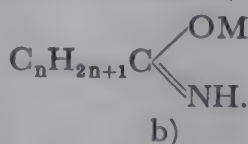
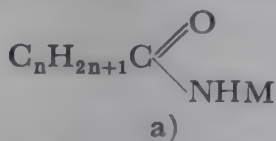
The esters of the carboxylic acids with phenols (see Ch. 28) appear to react particularly easily as a rule with ammonia to give amides.

The basic character of the —NH₂ group is to a large extent neutralized by the acyl radical with which it is combined in the amides. They can, however, still form addition compounds with mineral acids, e.g. CH₃CONH₂·HCl, but these are very unstable, and are hydrolysed by water. The acid amides react neutral to litmus. On the other hand they are capable of forming metal salts. The sodium salts, produced from acid amides and sodamide in ether, are decomposed again even by water. Certain silver, magnesium, and zinc derivatives behave in the same way. The mercury salts are more stable.

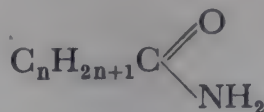
Since two tautomeric formulæ have to be considered in the case of the amides:



one type of salt may have formula (a), the other formula (b):



For the mercury salts, e.g. (CH₃CONH)₂Hg, the first formula is probably correct. Refractometric, cryoscopic, and conductivity measurements agree determinative with

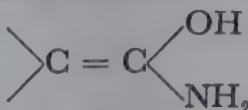


as the constitution of the free acid amides.

By heating with mineral acids the amides are hydrolysed to carboxylic acids. Alkalis act in a similar way, but more slowly:



The hydrolysis of amides by alkali possibly takes place via enolamine forms:



which are formed from >CHCONH_2 by the action of the alkali. One argument in favour of this view is the racemization of optically active compounds $\text{RR}'\text{CHCONH}_2$ during alkaline hydrolysis.

The re-formation of the carboxylic acid from the amides can be brought about by means of nitrous acid, a reaction which is analogous to the formation of primary alcohols from amines:



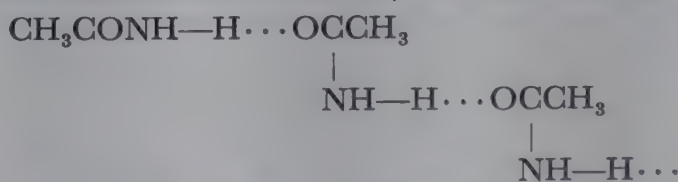
By the reduction of the amides with sodium in alcohol, primary alcohols are formed, though the reaction often does not proceed smoothly:



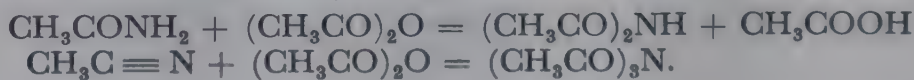
Of great preparative value is the Hofmann reaction for obtaining amines from the amides, the mechanism of which has been considered on p. 130.

The acid amides are, with the exception of the first member, solid at room temperature. The lower compounds dissolve readily in water, the higher ones are almost insoluble. Their odour is usually unpleasant, but improves with the purity of the substance. FORM-AMIDE, HCONH_2 , m.p. 1.8° ; ACETAMIDE, CH_3CONH_2 , m.p. 82° ; b.p. 222° ; PROPION-AMIDE, $\text{C}_2\text{H}_5\text{CONH}_2$, m.p. 79° , b.p. 213° ; PALMITIC ACID AMIDE, $\text{C}_{15}\text{H}_{31}\text{CONH}_2$, m.p. 104° ; STEARIC ACID AMIDE, $\text{C}_{17}\text{H}_{35}\text{CONH}_2$, m.p. 109° .

Acid amides and likewise their related carbamic acid esters (q.v.), urea (q.v.), and polypeptides, containing at least *one* hydrogen atom on the nitrogen atom, are more or less strongly associated. The association is effected by the imide-hydrogen ("hydrogen bonds"):



There are also *secondary amides*, $(\text{C}_n\text{H}_{2n+1}\text{CO})_2\text{NH}$, and *tertiary amides*, $(\text{C}_n\text{H}_{2n+1}\text{CO})_3\text{N}$, which are, however, of little interest. The former are produced, for example, by heating the primary amides with acetic anhydride, the latter by the action of acetic anhydride on nitriles:

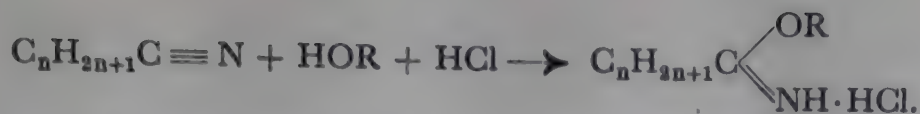


Imido-ethers, $\text{C}_n\text{H}_{2n+1}\text{C} \begin{array}{l} \nearrow \text{OR} \\ \searrow \text{NH} \end{array}$. **Amidines**, $\text{C}_n\text{H}_{2n+1}\text{C} \begin{array}{l} \nearrow \text{NH}_2 \\ \searrow \text{NH} \end{array}$

The imido-ethers (or imido esters) are derived from the tautomeric form of

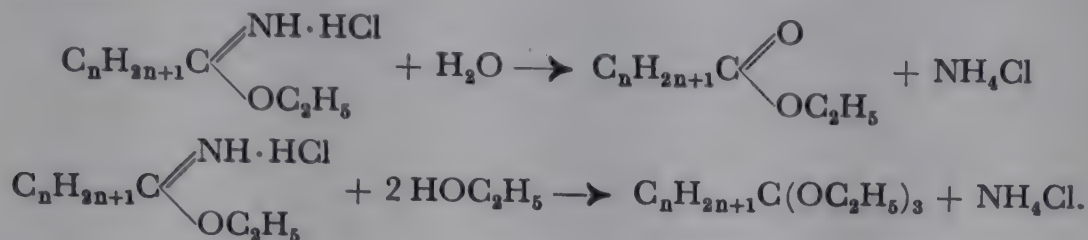
the acid amides $\text{C}_n\text{H}_{2n+1}\text{C} \begin{array}{l} \nearrow \text{OH} \\ \searrow \text{NH} \end{array}$. They are produced as the hydrochlorides if

hydrogen chloride acts upon a dry mixture of a nitrile and an alcohol:

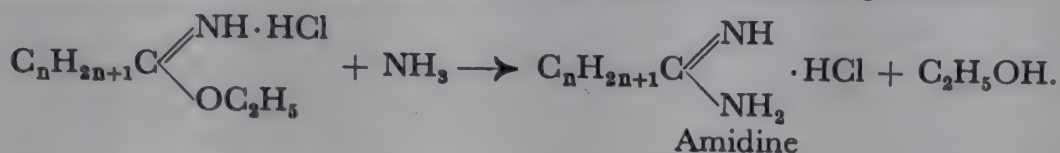


The reaction thus consists in the addition of the alcohol to the cyanide group.

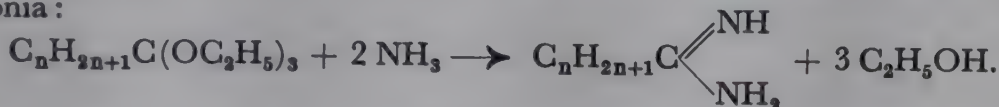
The hydrochlorides of the imido-ethers crystallize well, and are readily soluble in water. The free imido-ethers can be obtained from them as basic, unstable oils. The hydrochlorides enter into a number of reactions. They are decomposed by water giving esters. Alcohol converts them into the ortho-esters of the carboxylic acids (q.v.) :



Alcoholic ammonia replaces the alkoxy-group. *Amidines* are produced :



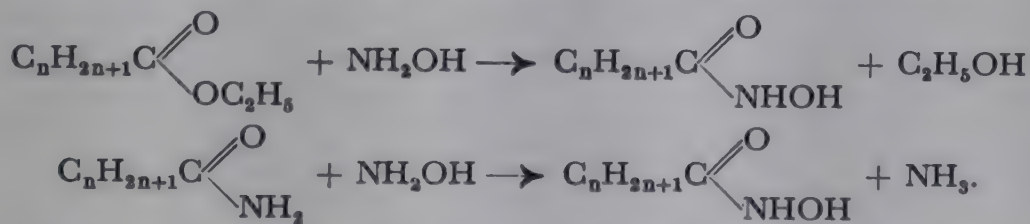
These are also obtainable from the esters of the ortho-carboxylic acids by the action of ammonia :



The amidines are strong, monacid bases. They form well-crystallized salts (hydrochlorides, nitrates). Even the nitrites are stable. The amino-group of the amidines thus does not react in the normal manner with nitrous acid. The amidines have been used in the synthesis of heterocyclic compounds. They will be met with again later in this connection.

Hydroxamic acids, $\text{C}_n\text{H}_{2n+1}\text{C} \begin{array}{l} \text{O} \\ \text{NHOH} \end{array}$

Hydroxamic acids are usually prepared by the action of hydroxylamine on the esters of the carboxylic acids. The action of hydroxylamine on acid amides, acid anhydrides, and the acid chlorides also gives hydroxamic acids :



It is of considerable interest to note that aldehydes combine with nitrohydroxylamine to give hydroxamic acids :



This reaction is used for the detection of small amounts of aldehydes ; for the hydroxamic acids in aqueous solution give an intense blood-red coloration with ferric chloride (formation of an internal complex salt) from which they can be recognized

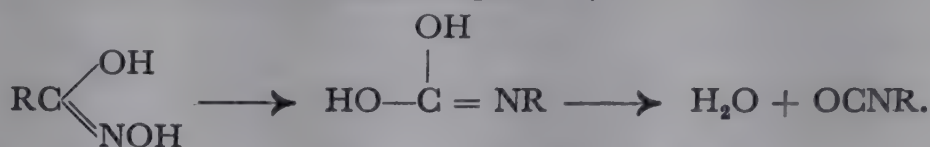
even in traces. Their green, difficultly soluble copper salts are also fairly characteristic.

It may also be noted that the hydroxamic acids belong to the classes of compounds which can exist in tautomeric forms. The tautomeric form is the hydroximic acid form (a):



Alkyl derivatives of these, the alkylhydroximic acids, are known.

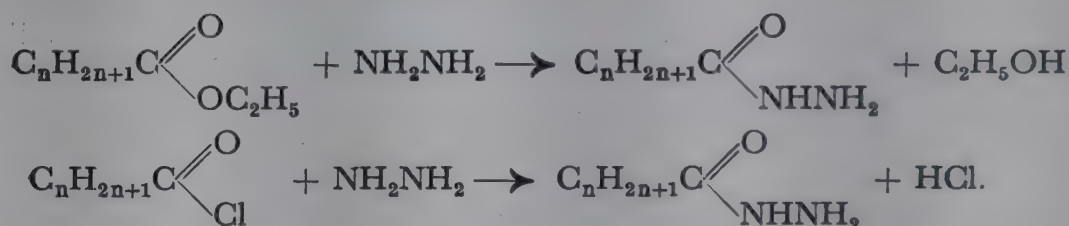
By the action of thionyl chloride the hydroxamic acids undergo a rearrangement (Lossen's rearrangement) which resembles those occurring in the Curtius and Hofmann degradations of acid azides and amides respectively:



Formhydroxamic acid, leaflets, m.p. 81–82°. Acethydroxamic acid, m.p. 88°.

Acid hydrazides. Acid azides. Hydrazidines.

The *acid hydrazides* have the formula $\text{C}_n\text{H}_{2n+1}\text{C} \begin{array}{l} \nearrow \text{O} \\ \searrow \text{NH} \cdot \text{NH}_2 \end{array}$. They can be obtained from the esters of the carboxylic acids, the acid chlorides, or anhydrides by the action of hydrazine (Curtius):



Hydrazides are basic, crystalline substances, soluble in water, which reduce Fehling's solution and ammoniacal silver nitrate.

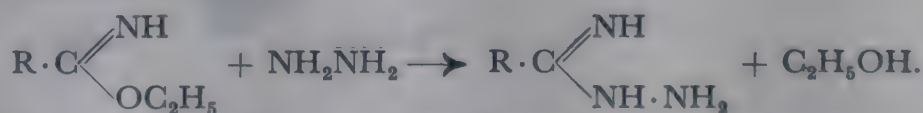
Their most important reaction is that with nitrous acid, which converts them into the acid azides, $\text{C}_n\text{H}_{2n+1}\text{CON}_3$, (Curtius):



Acid azides are crystalline (but sometimes liquid) compounds, fairly unstable. Some of them explode weakly when put into a flame. The important Curtius conversion of carboxylic acids into amines takes place through these compounds (see p. 130.)

Compounds corresponding in structure to the amidines are the *Hydrazidines*

$\text{R} \cdot \text{C} \begin{array}{l} \nearrow \text{NH} \\ \searrow \text{NH} \cdot \text{NH}_2 \end{array}$. They are formed from imido-ethers and hydrazine and were investigated chiefly in the aromatic series:



They have often been successfully used in the syntheses of heterocyclic compounds.

Section IV

Compounds with tetravalent functions

CHAPTER 13. SIMPLE TETRASUBSTITUTION PRODUCTS OF METHANE

Tetravalent halogen function

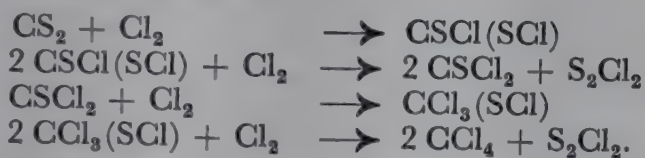
Organic compounds, in which four substituents different from hydrogen are attached to the same carbon atom, can only be derived from methane. The number of such substances is therefore limited.

CARBON TETRACHLORIDE, CCl_4 . The direct combination of carbon with chlorine is not possible. On the other hand, it is possible to obtain *carbon tetrachloride* by the further chlorination of chloroform. The preparation of the compound from methane and chlorine is described in a number of patents. Light, metals, salts of iron and copper, are used as catalysts.

The older procedures for making carbon tetrachloride start with carbon disulphide (Kolbe, A. W. Hofmann). This combines with chlorine in the presence of halogen carriers, e.g. antimony pentachloride, aluminium chloride, iodine, etc., to give carbon tetrachloride and sulphur monochloride:



The reaction probably takes place through several intermediate stages, which according to P. Klason are as follows:

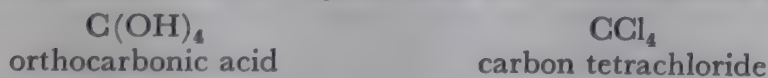


Another method of practical importance makes use of the chlorination of carbon disulphide with sulphur monochloride. Iron, ferric chloride, or other metals are used as catalysts (Müller and Dubois, Urbain). The reaction takes place with elimination of sulphur:



Carbon tetrachloride is a colourless liquid, with a sweetish smell resembling that of chloroform. It boils at 77° , and melts at -24° . The vapour is non-inflammable and non-explosive. These properties give carbon tetrachloride definite advantages over other inflammable solvents such as ether, petrol, and similar liquids. It is an excellent solvent for resins, fats, waxes, and lacquers, and has attained considerable technical importance for this purpose. It is also used as a diluent in numerous chemical reactions, e.g. chlorinations, and as a fire-extinguisher.

Carbon tetrachloride can be regarded as the tetrachloride of orthocarbonic acid:



In fact, esters of orthocarbonic acid can be obtained from this substance by treating it with sodium alcoholates:



A remarkable observation is that of Birkenbach and Goubeau who found that carbon tetrachloride and silver perchlorate, in the presence of traces of hydrogen chloride form trichloromethyl perchlorate, $\text{CCl}_3 \cdot \text{ClO}_4$, a colourless liquid (m.p. about -55°), which immediately gives perchloric acid with water and reacts vigorously with organic substances.

CARBON TETRABROMIDE, CBr_4 . This compound is formed in an analogous way to the preceding one by the action of carbon disulphide on bromine, or from acetone by the action of excess sodium hypobromite. M.p. 94° , b.p. 189° . Up to the present no practical use has been found for this compound.

CARBON TETRAIODIDE, CI_4 . This compound is obtained, though not very smoothly, by the action of the iodides of aluminium, calcium, or boron on carbon tetrachloride, or by heating the latter with methyl iodide and aluminium chloride. Carbon tetraiodide forms dark red crystals and is very unstable.

CARBON TETRAFLUORIDE, CF_4 . This compound is readily formed by the direct combination of carbon and fluorine; C_3F_8 , C_4F_{10} , C_5F_{12} , etc. are formed at the same time. Another method of obtaining carbon tetrafluoride is by the action of silver fluoride on carbon tetrachloride. It is a colourless, odourless gas, which is without action on water, and is not attacked by aqueous potassium hydroxide solutions. Its b.p. is -126° , m.p. -191° .

Halogen-, sulphur-, and nitrogen-containing derivatives of carbonic acid

From carbon dioxide, CO_2 , carbonic acid, $\text{OC}(\text{OH})_2$, and orthocarbonic acid $\text{C}(\text{OH})_4$, a large number of important compounds are derived in which the oxygen of the carbonic acid has been completely or partially substituted by halogen, sulphur, or nitrogen-containing radicals. They can, of course, also be regarded as derivatives of methane, which justifies their consideration at this place.

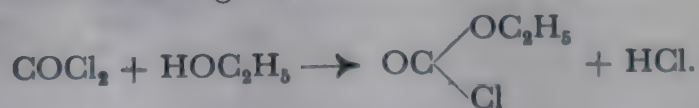
Phosgene, carbonyl chloride, COCl_2 . *Phosgene*, the chloride of carbonic acid, is produced, according to an observation due to Davy, by exposing a mixture of carbon monoxide and chlorine to light:



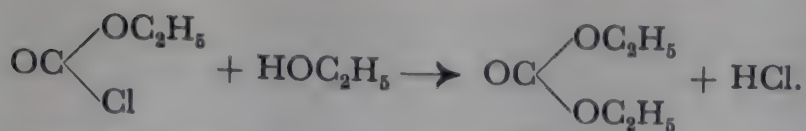
The process is reversible. At higher temperatures there is an equilibrium between the CO and Cl_2 on the one side, and the COCl_2 on the other, and at 800° , phosgene is completely broken down into its components.

In technical methods of preparation, finely divided wood- or bone-charcoal is used to catalyse the combination of carbon monoxide and chlorine (Paternò). Equimolecular quantities of carbon monoxide and chlorine are made to react at 200° .

Phosgene is a suffocating, very poisonous gas. (Note its formation by the oxidation of chloroform (see p. 182) and the dangerous consequences if such chloroform is used as an anæsthetic). It boils at 8° . It is readily soluble in benzene and toluene, but is decomposed by water into carbon dioxide and hydrogen chloride. With alcohol it first gives chlorocarbonic ester:



The chlorine atom of the chlorocarbonic ester is then much more slowly replaced by the ethoxy radical:



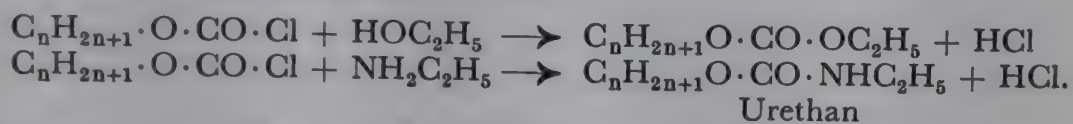
Phosgene is used for the introduction of the carbonate radical into other substances. It has special importance in the dyeing industry for the synthesis of Michler's ketone, which is formed from dimethylaniline and phosgene, and is the starting point for the preparation of numerous basic triphenylmethane dyes.

Carbonyl chloride combines with molten aniline hydrochloride to form the important reagent, *phenyl isocyanate*:

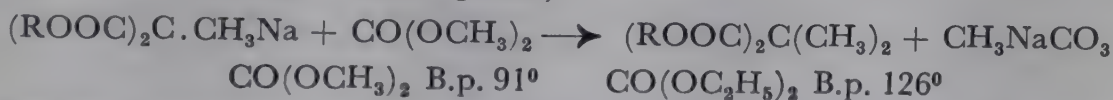


Chlorocarbonic esters, $\text{ClCOOC}_n\text{H}_{2n+1}$, the esters of the semi-chloride of carbonic acid, are formed, as mentioned above, from phosgene and alcohols. The reaction is made to take place in the cold to avoid the replacement of the second chlorine atom.

The chlorocarbonic esters are volatile liquids with a suffocating smell. Their halogen atom is, like that, of other acid chlorides, very mobile. These compounds are therefore suitable for the introduction of the esterified carboxyl group, $-\text{COOC}_n\text{H}_{2n+1}$, into alcohols, phenols, amines, reactive methylene compounds, etc. With alcohols they form the *neutral esters of carbonic acid*, and with amines, *esters of carbamic acid*, the so-called urethans:



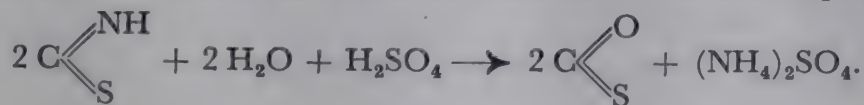
The *diesters of carbonic acid* are neutral liquids, slightly soluble in water and having an ethereal smell. They may sometimes serve as alkylating agents, for example in the reaction with sodium monoalkylmalonic esters yielding dialkylmalonic esters (Wallingford and Jones):



Carbon oxysulphide, COS . *Carbon oxysulphide* is formed from carbon monoxide and sulphur at a dull red heat:



It can also be obtained from carbon disulphide by various processes of partial hydrolysis, e.g. by heating with water in autoclaves. The hydrolysis of thiocyanic acid salts with sulphuric acid is a suitable reaction to use for its preparation:



The hydrolysis of mustard oils (isothiocyanic esters, see p. 240) with concentrated sulphuric acid also yields carbon oxysulphide, in addition to primary amines.

Carbon oxysulphide is a colourless gas, which burns with a blue flame. Boiling point -47.5° . It is gradually hydrolysed by water to carbon dioxide and hydrogen sulphide.

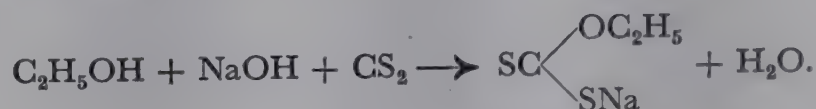
Carbon disulphide, CS_2 . *Carbon disulphide*, the sulphur compound corresponding to carbon dioxide, is prepared by passing sulphur vapour over

heated coke (800–900°). The process is reversible. At very high temperatures, carbon disulphide breaks down again into its elements.



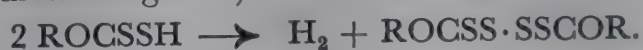
The compound is a very highly refracting liquid. Its smell is not unpleasant, but is usually impaired by impurities. It boils at 46°, and melts at –112.8°. The vapour of carbon disulphide is poisonous, and is easily inflammable (care required in working with it). The flame is blue.

The ease with which carbon disulphide dissolves fats, oils, and resins gives it technical importance as an extracting agent. Carbon disulphide is also used in the preparation of carbon tetrachloride (see p. 227), thiocyanates, and thiourea, for vulcanizing rubber, and, on account of its toxicity, for the extermination of plant pests. Its chief use, however, is in the *viscose* process for manufacturing artificial silk. The formation of viscose rayon from cellulose depends on a general reaction of carbon disulphide with alcohols. It combines with them in the presence of alkalis to give “*xanthates*” (or “*xanthogenates*”) ester-salts of *dithiocarbonic acid*, which are readily soluble in water:



The starting product of viscose rayon manufacture is *cellulose xanthate*.

The alkali salts of the xanthic acids crystallize well and dissolve readily in water. The heavy-metal salts, e.g. the cuprous salt, are yellow in colour (hence the name *xanthate*), and are insoluble. The free xanthic acids, $\text{C}_n\text{H}_{2n+1}\text{OCSSH}$, are also known as *oils*, which are very unstable, and decompose spontaneously, particularly in the presence of water, into alcohols and carbon disulphide. The *xanthates* are powerful reducing agents. They give up hydrogen and are converted into *dixanthides* (or “*dixanthogens*”):



Carbamic acid and its derivatives

Free Carbamic acid, H_2NCOOH , is not known, but its salts, esters, and amides exist.

Of the *salts*, ammonium carbamate is the most easily obtainable. It is formed as a crystalline solid by the action of dry carbon dioxide on dry ammonia:



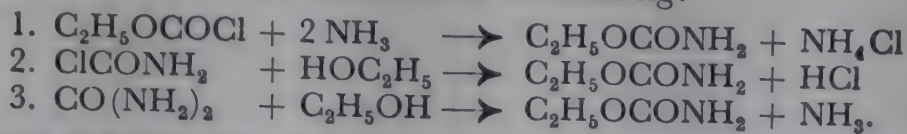
Aqueous solutions of ammonium carbonate, on the other hand, contain some ammonium carbamate. The calcium and barium salts of carbamic acid are readily soluble, and hence can be used to separate the carbonate from the carbamate.

Carbamyl chloride, $\text{H}_2\text{N} \cdot \text{COCl}$, also known as *urea chloride*, is obtained by heating phosgene and ammonium chloride together to 200–300°.

Important derivatives of carbamic acid are met with in its esters, the *Urethans*, $\text{NH}_2 \cdot \text{COOC}_n\text{H}_{2n+1}$. They are well-crystallized, stable compounds, some of which have been used as *sedatives* and *hypnotics*, e.g. the ethyl ester of carbamic acid, commonly known as *urethan* (m.p. 48.5°; b.p. 184°), the ester with amylene hydrate, *aponal*, $\text{H}_2\text{NCOOC}(\text{CH}_3)_2(\text{C}_2\text{H}_5)$, that with methylpropyl carbi-

nol, *hedonal*, $\text{H}_2\text{NCOOCH}(\text{CH}_3)(\text{C}_3\text{H}_7)$; phenylurethan, $\text{C}_6\text{H}_5\text{NHCOOC}_2\text{H}_5$, is an antipyretic (*euphorin*), like analogous urethans of the aromatic series.

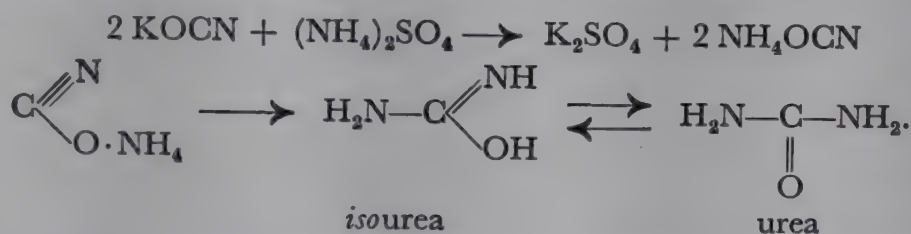
The esters of carbamic acid can be prepared in various ways, from chloro-carbonic esters and ammonia, from carbamyl chloride and alcohols, and particularly from urea, which reacts with alcohols on heating:



Urea¹, NH_2CONH_2 . Of all the derivatives of carbamic acid, *urea*, its amide, is the most interesting and most important. It is the chief final product of nitrogen metabolism in man and mammals, being formed in the decomposition of proteins, and excreted in the urine (hence the name). An adult excretes 28–30 gms daily. The compound also occurs in plants, but only in small quantities.

After the discovery of urea in urine by Rouelle in 1773, it was later more fully investigated by Fourcroy and Vauquelin, and Prout. It was synthesized in 1828 from ammonium cyanate by Wöhler, this, with the successful synthesis of oxalic acid from cyanogen carried out shortly before, being the first synthetic preparation of a substance produced in the living organism.

The rearrangement that ammonium cyanate undergoes on heating may be still used to-day for the technical production of urea. An aqueous solution of potassium cyanate and ammonium sulphate is evaporated, and the urea formed can be extracted with alcohol or separated by crystallization.

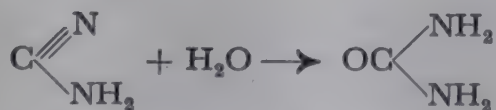


In more recent times, however, another process has been introduced for the commercial preparation of urea. Ammonia is made to react with carbon dioxide to give ammonium carbamate (see above) and this is heated under pressure, breaking down into water and urea:

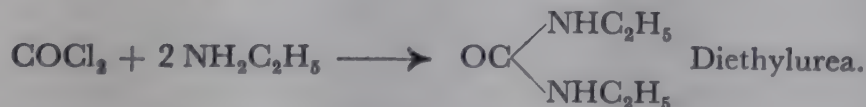


This preparation of urea is carried out in conjunction with the synthesis of ammonia from its elements.

The addition of water to commercial cyanamide (see p. 236) which occurs when mineral acids act upon it, is also a practicable method of synthesizing urea on a large scale:



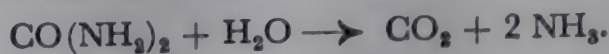
Whilst the interaction of phosgene and ammonia and its derivatives proceeds very smoothly, it is too expensive for the technical preparation of urea, and is more often used for the preparation of *derivatives* of urea:



¹ E. A. WERNER, *The Chemistry of Urea*, London, (1923).

Urea crystallizes in prisms, can be sublimed in a vacuum, and is readily soluble in water and alcohol, giving neutral solutions. Its melting point is 133°.

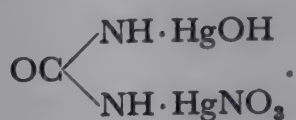
On heating with acids or alkalis it is hydrolysed to carbon dioxide and ammonia. The enzymes, the so-called *ureases*, (occurring in micro-organisms, soya beans, etc.) bring about this hydrolysis even at ordinary temperatures:



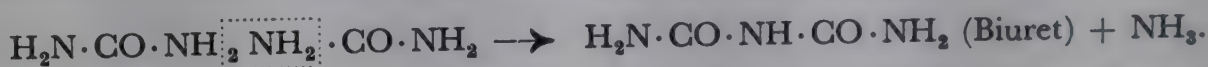
Nitrous acid reacts with urea to give carbon dioxide, water, and nitrogen (method of destroying nitrous acid):



As an acid amide urea can form salts on the one hand with mineral acids, and on the other with metals. The nitrate, $\text{CO}(\text{NH}_2)_2 \cdot \text{HNO}_3$, and the oxalate, $[\text{CO}(\text{NH}_2)_2]_2 \cdot \text{H}_2\text{O}_4\text{C}_2$, are difficultly soluble, and crystallize well. They may be formulated partly as ammonium and partly as oxonium salts, $\text{O}_3\text{N}[\text{HOC}(\text{NH}_2)_2]$. A mercury compound of urea can be precipitated by the action of mercuric nitrate on urea. It also has a low solubility and is formulated as:



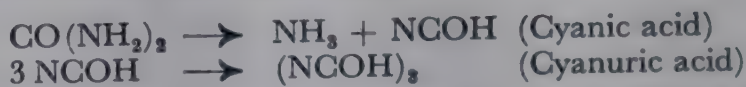
The reactions which urea undergoes on heating are of interest. If heated slowly to 150–160°, ammonia is eliminated and *biuret* (m.p. 193°) is formed:



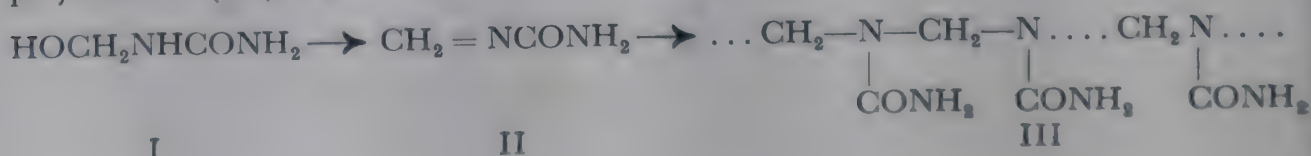
Biuret may be regarded as the amide of *allophanic acid*, $\text{H}_2\text{N} \cdot \text{CO} \cdot \text{NH} \cdot \text{COOH}$, itself a *ureide* (urea derivative) of *carbonic acid*.

Biuret is characterized by the fact that it gives an intense violet coloration with copper salts in alkaline solution, which depends on the formation of a complex copper salt. This reaction, known as the *biuret reaction*, is characteristic of many substances which have more than one amide radical $-\text{CO} \cdot \text{NH}_2$, or similar groups in the molecule (a positive reaction is also given by aminoalcohols with terminal or middle aminohydroxyethylene radicals $-\text{CHNH}_2 \cdot \text{CHOH}-$). It is likewise given by the proteins and is used for the detection of these compounds.

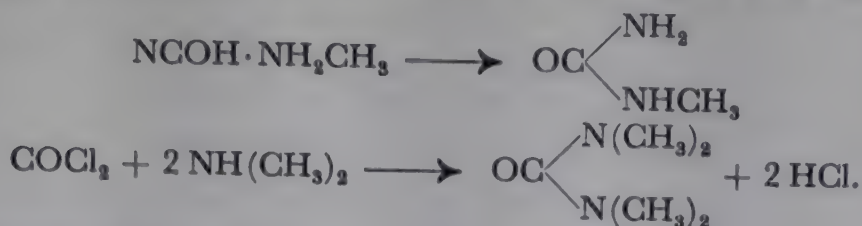
If the heating is more rapid, and is taken to a somewhat higher temperature, the chief product is *cyanic acid*, which, however, polymerizes at this temperature to the trimolecular *cyanuric acid* (see p. 237):



Urea is extensively used at present as a fertilizer. It is also used as a stabilizer for nitrocellulose, and in medicine as a diuretic. A series of hypnotics (veronal, propanal, dial, luminal) are prepared with the aid of urea, as well as the sedatives adaline (bromodiethyl-acetylurea) and brominal (α -bromoisovaleryl-urea), and the iodine preparation iodival (α -iodoisovaleryl-urea). The urea-formaldehyde resins, as technically produced, are obtained directly from the starting materials without catalysts or by the addition of bases (NH_3) or acids. The first reaction product is probably the methylolurea (I), which is further transformed into methyleneurea (II) by the loss of water. From the latter the polymerizate (III) is formed:



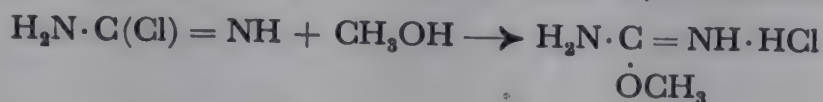
ALKYLATED UREAS are obtained in a similar way to urea. They are formed by heating alkylated ammonium cyanates, or from phosgene and alkylamines:



More interesting than these compounds, which have few special characteristics other than those of urea, are the alkyl derivatives of the tautomeric form of urea, $\text{H}_2\text{N}-\text{C}=\text{NH}$, known as "isourea". Whilst urea itself is known in only one form,



probably corresponding to the formula $\text{H}_2\text{N} \cdot \text{CO} \cdot \text{NH}_2$, it has been possible to make O-alkyl-ethers of isourea from cyanamide hydrochloride and alcohols (Stieglitz):

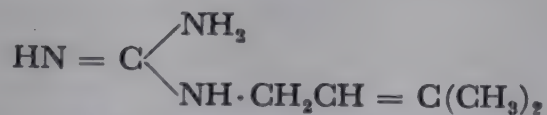


These share the group $-\text{C} \begin{array}{l} \text{NH} \\ \text{OCH}_3 \end{array}$ with the imido-ethers, and are, like them, strong bases.

ACID DERIVATIVES OF UREA, $\text{C}_n\text{H}_{2n+1}\text{CO} \cdot \text{NHCONH}_2$. These compounds, in which one hydrogen atom of urea is substituted by an acyl group, are called *ureides*. The simple fatty acid ureides are of little importance. Some ureides containing bromine and iodine have been mentioned above as medicines (adalin, bromural, iodival). The ureides of certain dicarboxylic acids, which will be dealt with later, are, however, important. See p. 279.

Guanidine, $\text{HN} = \text{C} \cdot (\text{NH}_2)_2$ (imidourea). This compound gets its name from *guanine*, a purine body (see Ch. 62) which is found, for example, in guano. Strecker discovered guanidine in the degradation of guanine. A guanidine derivative (arginine) is found in proteins, and others (creatinine) in muscle juice and elsewhere, and a further one (agmatine) in *Secale cornutum* and herring sperm.

Another naturally-occurring guanidine derivative is *galegine*, isoamylene-diguanidine:

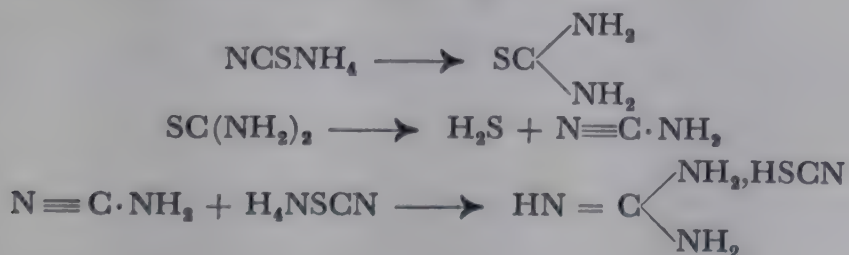


which occurs in the seeds and leaves of *Galega officinalis*. *Synthaline*, decamethylene-

diguanidine, $\text{H}_2\text{N} \cdot \text{C}(=\text{NH}) \cdot \text{NH} \cdot (\text{CH}_2)_{10} \cdot \text{NH} \cdot (\text{HN} =) \text{C} \cdot \text{NH}_2$,

serves medical purposes (diabetes).

Guanidine can be prepared by heating ammonium thiocyanate to 180° . This rearranges first into thiourea, which breaks down into hydrogen sulphide and cyanamide, and the cyanamide combines as it is formed with unchanged ammonium thiocyanate to guanidine thiocyanate:



Another convenient synthesis of guanidine depends on the addition of ammonia to cyanamide:



A further synthesis is based on the interaction of esters of orthocarboxylic acids and ammonia:

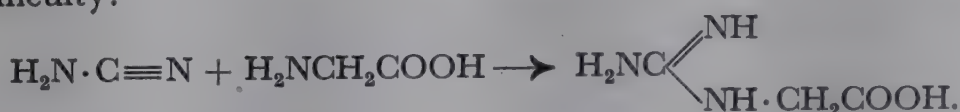


Guanidine is a very strong, monacid base, colourless, crystalline, and very hygroscopic. The nitrate and picrate are difficultly soluble and serve to characterize the substance.

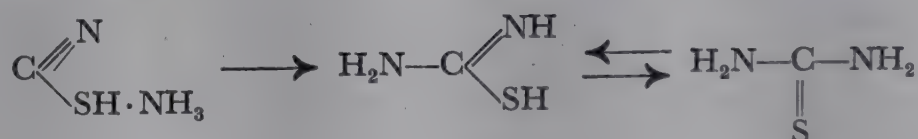
On heating with baryta-water, guanidine is hydrolysed to urea and ammonia:



The usual method of preparing guanidine derivatives is the addition of amines to cyanamide, a method which will also give the more complex compounds without difficulty:



Thiourea, $\text{CS}(\text{NH}_2)_2$. *Thiourea* shows many similarities to urea in chemical behaviour. It can be obtained by a method analogous to Wöhler's synthesis of urea by heating ammonium thiocyanate. The temperature in the latter case, however, must be somewhat higher, being in the neighbourhood of the melting point of ammonium thiocyanate:

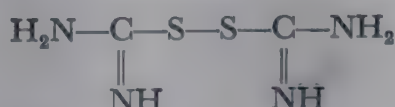


Another useful method of making thiourea depends on the addition of hydrogen sulphide (or ammonium sulphide) to cyanamide.

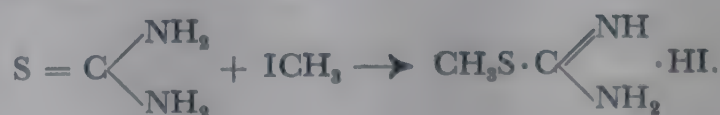
Thiourea is a stable substance which crystallizes well, and is fairly easily soluble in water. It melts at 180° . Like urea it forms easily dissociated addition compounds with mineral acids, and it forms coordination compounds with many metal salts. Although known in only one form itself, it can react in two tautomeric forms:



This is shown, for instance, by its oxidation with permanganate which gives disulphides of the type:

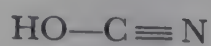


The alkyl compounds are also derived from "iso-" or "pseudo"-thiourea. They are made by the addition of alkyl halides to thiourea, and must therefore be formulated as S-alkyl-pseudothioureas:



Cyanic acid

CYANIC ACID belongs to the simple acids which react as tautomeric substances. The two formulæ



I

Cyanic acid



II

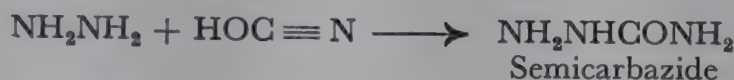
Isocyanic acid

must be considered, each of which explains certain reactions cyanic acid. Probably, liquid cyanic acid consists of an allelotropic mixture of the two isomerides. The Raman spectrum (see p. 381) supports the *iso*-form, $\text{O}=\text{C}=\text{NH}$, as does also the addition of HF and HBr , which leads to carbamic acid halides, H_2NCOX .

When urea is heated a trimeric derivative of cyanic acid, cyanuric acid (cf. p. 237) is formed. If the latter is heated in a current of carbon dioxide, it breaks down into cyanic acid, a very volatile, corrosive, highly unstable liquid, which can only be kept for a short time in the cold. Even at 0° a fresh polymerization occurs, partly to give cyanuric acid again, but chiefly with the formation of another trimeric compound "*cyamelide*".

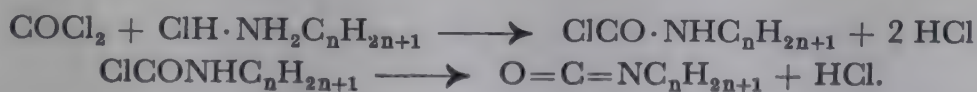
The salts of the acid, the *cyanates*, are more easily prepared. The potassium salt, KOCN , is made technically by the oxidation of potassium cyanide with potassium dichromate. Other cyanates are prepared from it. Ammonium cyanate, as has been already mentioned, plays an important part in Wöhler's synthesis of urea.

Cyanic acid is very reactive. With alcohols it reacts to give esters of carbamic acid, with amines it gives urea derivatives, with hydrazine it gives *semicarbazide*. This is the best way of preparing this compound:



Another method of making semicarbazide is by the electrolytic reduction of *nitrourea*.

The *alkyl isocyanates*, $\text{C}_n\text{H}_{2n+1}\text{N}=\text{C}=\text{O}$, are derived from the *iso*-form of the acid. They occur as intermediate products in the Hofmann degradation of amides (see p. 130) and the Curtius degradation of azides (see p. 130) and can be prepared from potassium cyanate and dialkyl sulphates, or from the hydrochlorides of primary amines and phosgene. The latter reaction leads first to the chlorides of the carbamic acids, which break down under the action of alkalis into hydrogen chloride and an isocyanate:



The constitution of the esters of *isocyanic acid* is given by their behaviour on alkaline hydrolysis. They are decomposed into primary amines and carbon dioxide, a reaction which, as mentioned above, led to the discovery of amines by Wurtz.



Alkyl *isocyanates* are volatile liquids with a pungent smell. They readily polymerize to *isocyanuric esters* (see p. 237).

CYANOGEN CHLORIDE, $\text{Cl}\cdot\text{C}\equiv\text{N}$, and CYANOGEN BROMIDE, $\text{Br}\cdot\text{C}\equiv\text{N}$, are to be considered as the chloride and bromide respectively of cyanic acid. These crystallize, but readily volatilize. They are exceedingly poisonous, and are ob-

tained by the action of chlorine and bromine on potassium cyanide or hydrocyanic acid:



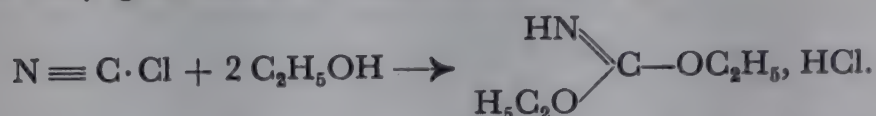
Of the two possible tautomeric formulæ:



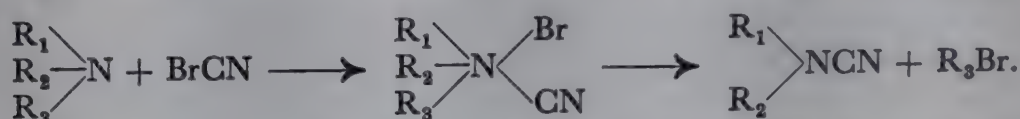
the first expresses better the numerous reactions of the cyanogen halides. For example, they react with ammonia and amines to give cyanamides:



With alcohol they give esters of iminocarbonic acids:



Cyanogen bromide has considerable importance in the *degradation of tertiary amines* (v. Braun). It combines with these to give first addition products which, on warming, break down into dialkylcyanamides and alkyl bromides:



Since the dialkylcyanamides can be easily hydrolysed to secondary amines this series of reactions leads to a degradation of the tertiary amines to secondary amines. An important special case of this is the breakdown of cyclic amines.

Cyanogen chloride, b.p. 15° , m.p. -6° ; cyanogen bromide, b.p. 61° , m.p. 52° ; Cyanogen iodide, ICN, is also known, m.p. 146° (in closed capillary).

CYANAMIDE, $\text{N} \equiv \text{C} \cdot \text{NH}_2$ or $\text{HN}=\text{C}=\text{NH}$. Cyanamide has been repeatedly met with in the earlier work. It can be regarded as the amide of cyanic acid, and may be represented by one of the foregoing formulæ. The sodium and calcium salts have become industrial products. Calcium cyanamide, or "*nitro-lime*" is obtained by heating technical calcium carbide in a current of nitrogen to about 1000° (Frank and Caro):



It has great importance as an artificial fertilizer. By the action of water it is successively converted in the soil into urea and ammonium carbonate, which serve as plant foods.

Sodium cyanamide, $\text{Na}_2\text{N}_2\text{C}$, is formed by heating sodamide with coke to about 400° :



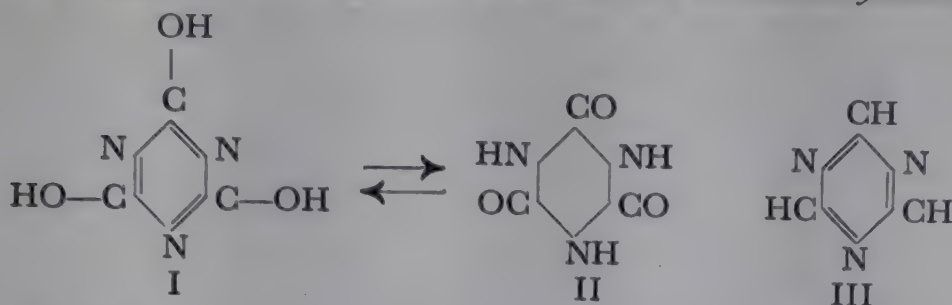
It is an intermediate product in the commercial synthesis of sodium cyanide (see p. 187) in the process used by the Gold- und Silberscheideanstalt, Frankfurt a. M.

Cyanamide can be obtained from commercial sodium cyanamide, e.g. by the action of sulphuric acid, the concentration of the latter being so chosen that all the water is retained as water of crystallization by the sodium sulphate produced. The free cyanamide is extracted from the reaction mass with ether or alcohol. It is readily soluble in water, and melts at 40° . On heating it melts and polymerizes

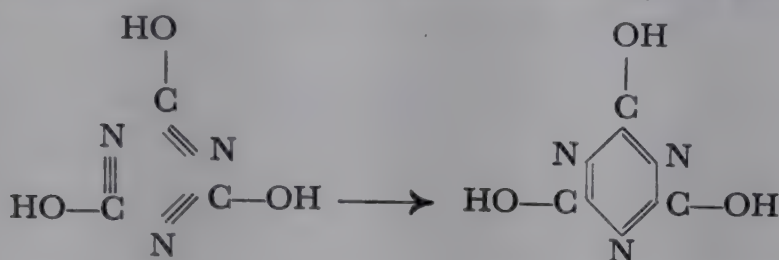
to dicyandiamide $\begin{array}{c} \text{NH} \cdot \text{CN} \\ \diagdown \\ \text{C} = \text{NH} \\ \diagup \\ \text{NH}_2 \end{array}$. The hydrolysis of cyanamide by acids or alkalis,

which gives urea, has been previously mentioned.

CYANURIC ACID, ISOCYANURIC ACID. It has often been emphasized that cyanic acid and its derivatives (*isocyanate* esters, cyanogen chloride, etc.) are capable of polymerization, and are easily converted into trimolecular compounds. For *cyanuric acid*, obtained from cyanic acid, two formulæ come under consideration (I and II), of which the first represents normal, the second *isocyanuric acid*:

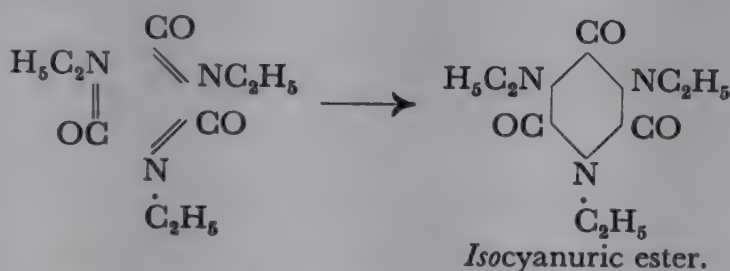


Cyanuric acid is thus a derivative of the heterocyclic compound III, which is called *symmetrical triazine*. The polymerization process which takes place when cyanic acid is converted into cyanuric acid is shown by the following equation:



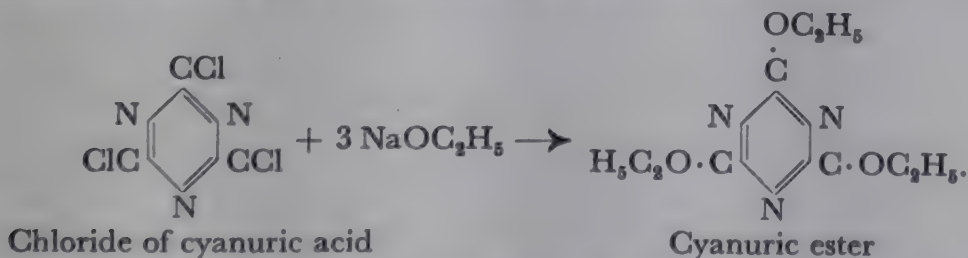
Cyanuric acid crystallizes well, is difficultly soluble in water, and shows a strong acid reaction.

The esters of *isocyanuric acid* are obtained by the polymerization of the *isocyanate* esters (see p. 235).

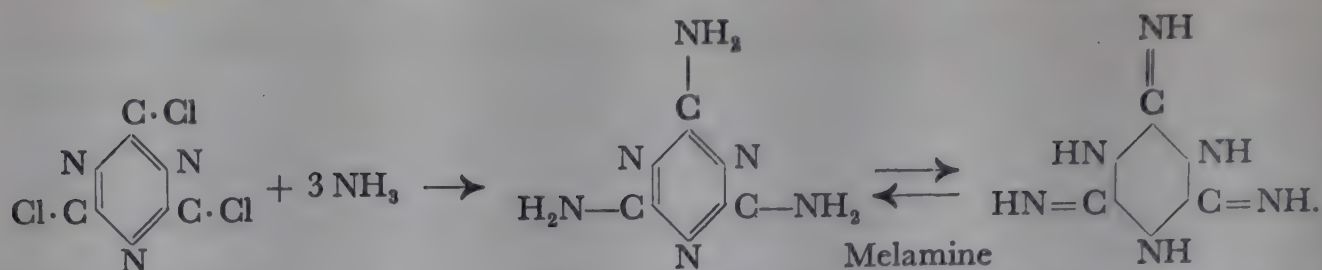


On heating with alkalis they are hydrolysed to carbon dioxide and primary amines. The reaction is conclusive in demonstrating the position of the alkyl radicals in the *isocyanuric* esters.

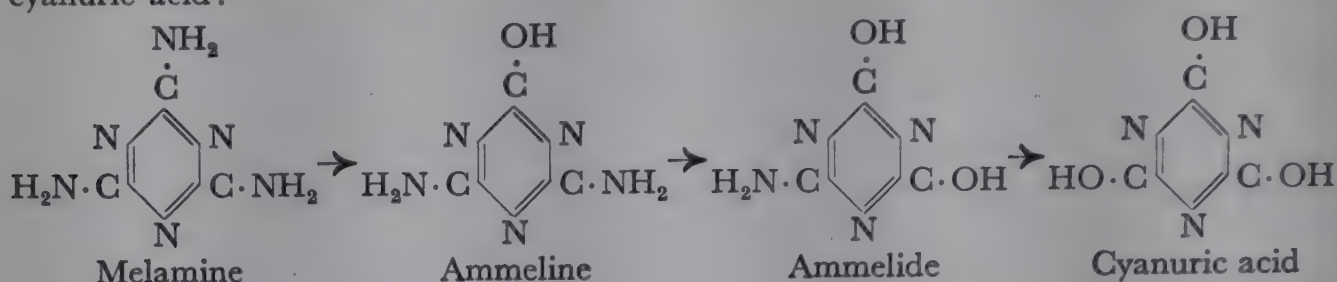
Esters of normal cyanuric acid are obtained from the chloride of cyanuric acid, the polymerization product of cyanogen chloride, and alcoholates. Their hydrolytic fission with acids or alkalis gives cyanuric acid and alcohols:



Finally, *melamine*, the *amide of cyanuric acid* will be considered. This is obtained by the action of ammonia on cyanuric acid chloride or cyanuric esters, or from cyanamide by polymerization (intermediate product dicyandiamide, see p. 236). The compound may be given the tautomeric formulæ:



Melamine is a fairly strong, crystalline, monacid base. Hydrolysis breaks it down to cyanuric acid:



Fulminic acid, $\text{C}=\text{N}-\text{OH}^1$

Mercury fulminate, or fulminating mercury, is formed, according to a process due to Howard, the discoverer of the salt, when an excess of alcohol reacts with a solution of mercury in nitric acid. The reaction is very violent, and oxides of nitrogen are evolved. The mercury fulminate is precipitated as an insoluble, white powder. Silver fulminate can be obtained in a similar way (fulminating silver).

Mercury fulminate explodes violently when struck or ignited. It is therefore used as a detonator for bombs, cartridges, and grenades. The percussion cap is filled with the substance, usually mixed with potassium chlorate, antimony sulphide, or trinitrotoluene. Silver fulminate is an even more powerful detonator.

The constitution of fulminic acid, which, as the formula shows is isomeric with cyanic acid, is based on the following reactions:

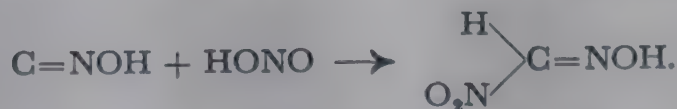
(a) Hydrolysis by hydrochloric acid gives formic acid and hydroxylamine (Carstanjen, Ehrenberg):



(b) Cold, concentrated hydrochloric acid adds on to fulminic acid; the oxime of formyl chloride is produced (Nef, Scholl), which probably is also an intermediate product in the hydrolysis of fulminic acid according to reaction (a):



(c) Nitrous acid adds on in a similar way to give methylnitrolic acid:

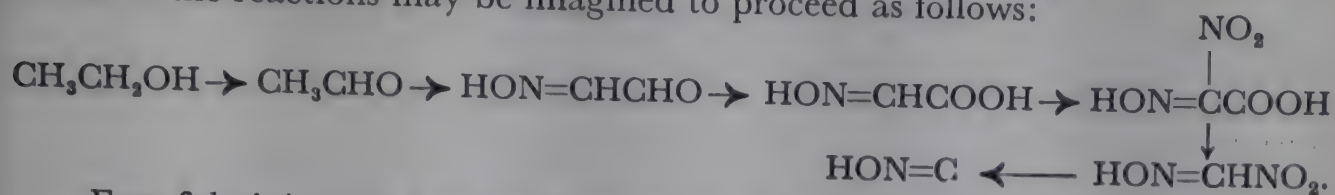


These reactions indicate fulminic acid to be an oxime of carbon monoxide, and agree with the commonly accepted formula, due to Nef. This is also confirmed by the smooth formation of fulminic acid from the oxime of formamide by the removal of ammonia by means of silver nitrate:

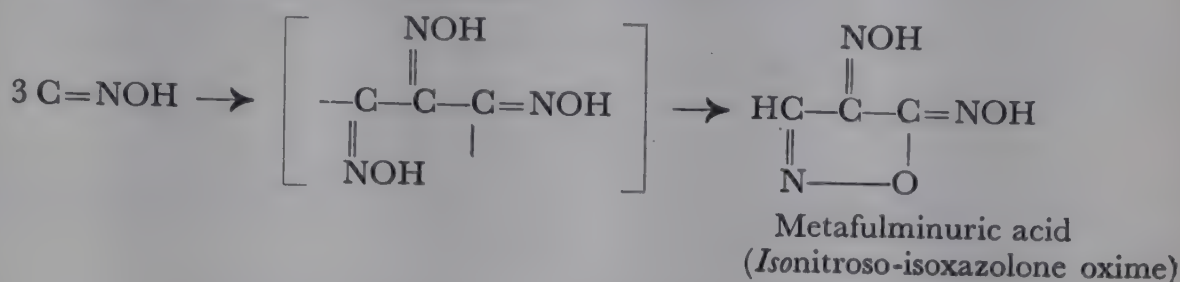


¹ See H. WIELAND, *Die Knallsäure*, Stuttgart, (1909).

Less clear are the reactions which lead from alcohol to fulminic acid as in the classical method of making mercury fulminate. According to Wieland the course of the reactions may be imagined to proceed as follows:

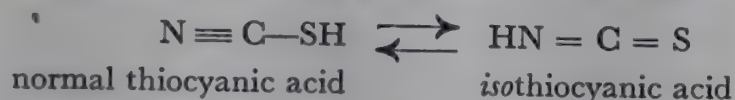


Free fulminic acid has only been obtained in solution at low temperatures. It has a penetrating smell, is very unstable, and polymerizes rapidly to "metafulminuric acid", a heterocyclic substance:



Thiocyanic acid

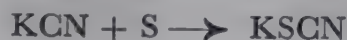
THIOCYANIC ACID differs from cyanic acid in that it contains sulphur instead of oxygen. It corresponds to one of the tautomeric formulæ:



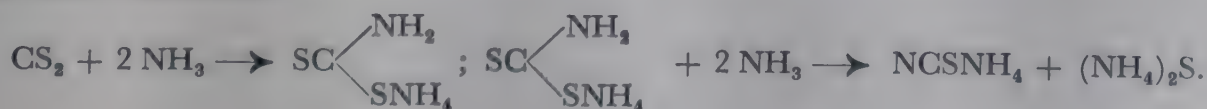
of which the first is commonly accepted for free thiocyanic acid. Alkyl compounds derived from both are known.

Alkali thiocyanates are present in small quantities in saliva, and can also be detected in various animal organs. In the vegetable kingdom, the esters of isothiocyanic acid, particularly, or *mustard oils*, are widely spread. The free acid is found in the onion.

The thiocyanate salts can easily be prepared by adding sulphur to a hot solution of the cyanides. An analogous process is the formation of thiocyanates in the contact catalyst used for purifying coal-gas:



Amongst the thiocyanate salts, that of ferric iron, $\text{Fe}(\text{SCN})_3$, is outstanding because of its intense red colour. A very sensitive analytical test for ferric iron on the one hand, and thiocyanates on the other, is based on its formation. On shaking with ether, in which ferric thiocyanate is readily soluble, the sensitivity of the test can be still further increased. Silver thiocyanate, AgSCN , is insoluble in acids. The Volhard silver titration (titration of a solution of a silver salt against potassium thiocyanate) depends on its formation. A ferric salt is used as indicator. After the silver thiocyanate has been completely precipitated, the ferric salt gives a red colour with an excess of potassium thiocyanate, due to ferric thiocyanate. Mercuric thiocyanate smells up considerably when burnt (Pharaoh's serpent). Ammonium thiocyanate is readily formed when carbon disulphide reacts with alcoholic ammonia:



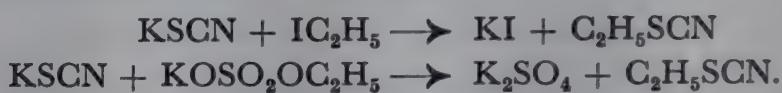
Free thiocyanic acid in concentrated solutions is only stable at low temperatures. It is liberated from strongly cooled potassium thiocyanate by means of sulphuric acid or potassium bisulphate, and is condensed in a receiver cooled with liquid air; snow-white crystals melting at -110° . It polymerizes even at -90 to -85° to a crystalline polymer, which can be depolymerized again. At about $+3^{\circ}$ the polymeric form decomposes (Birkenbach).

The dilute aqueous solutions of thiocyanic acid are considerably more stable. The acid is strongly dissociated. It is therefore a strong acid, approaching in this respect the mineral acids.

ESTERS OF NORMAL THIOCYANIC ACID, $C_nH_{2n+1}SCN$. The formation of these compounds from mercaptides and cyanogen chloride is a proof of their constitution:



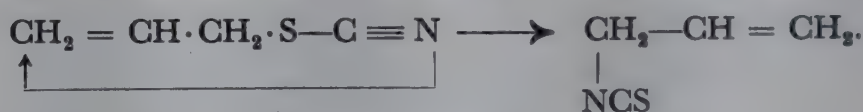
The usual method of preparation is by the alkylation of potassium thiocyanate with alkyl halides or alkyl hydrogen sulphates:



The esters of thiocyanic acid are liquids which can be distilled, and which have a garlic-like odour. Their most notable property is their isomerization at higher temperatures to the mustard oils:



This transformation occurs especially readily with allyl thiocyanate, the isomerization probably being due to a wandering of the thiocyanate radical (Billeter):

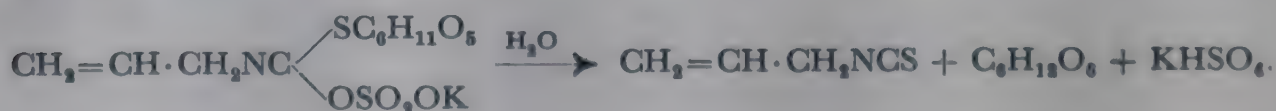


Some alkyl thiocyanates are used as plant insecticides.

ESTERS OF ISOTHIOCYANIC ACID. *Mustard oils*, $C_nH_{2n+1}N=C=S$. The production of the mustard oils from primary amines, carbon disulphide, and metal salts has already been referred to on p. 132. Their formation from the esters of normal thiocyanic acid was mentioned just above. They can be obtained from isonitriles by addition of sulphur:



The mustard oils have a pungent smell, from which they take their name. Many of them occur either free, or as glycosides, combined with sugars and other substances, in plants. By means of enzymes, which these plants produce, the mustard oil glycosides are hydrolysed, and the liberated mustard oil can be obtained by steam-distillation. The sulphur-containing glycoside of the black mustard (*Sinapis nigra* L.) is "*potassium myricate*". It is hydrolysed by acids or the enzyme myrosin (from mustard seed) into glucose, potassium bisulphate, and allyl isothiocyanate:



ALLYL ISOTHIOCYANATE also occurs in horse-radish and other plants. Optically active, secondary BUTYL ISOTHIOCYANATE, $(C_2H_5)(CH_3)CHNCS$, is contained in the oil of spoon-wort (*Cochlearia*) and in that of *Cardamine amara*. CROTYL ISOTHIOCYANATE, C_4H_7NCS , is found in rape-seed; CHEIROLINE, $CH_3SO_2(CH_2)_3NCS$, in wallflowers (*Cheiranthus*); ERY-SOLINE, $CH_3SO_2(CH_2)_4NCS$, in the seeds of *Erysimum Perowskianum*. The compound *p*-HYDROXYBENZYL ISOTHIOCYANATE, $HOC_6H_4 \cdot CH_2NCS$, obtained by hydrolysis of sinalbin, the glycoside present in white mustard, is an aromatic isothiocyanate, as is also β -PHENYLETHYL ISOTHIOCYANATE, $C_6H_5CH_2CH_2NCS$, found in *Nasturtium officinale*, *Tropaeolum majus*, and turnip.

Allyl isothiocyanate is used in medicine in place of mustard poultices.

CH_3NCS , b.p. 119° ; C_2H_5NCS , b.p. 133° ; C_3H_7NCS , b.p. 153° ; $n-C_4H_9NCS$, b.p. 167° ; $CH_2=CHCH_2NCS$, b.p. 150° ; $(CH_3)(C_2H_5)CHNCS$, b.p. 159° .

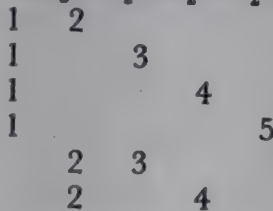
Section V

Compounds with two functions in the molecule

CHAPTER 14. COMPOUNDS WITH TWO MONOVALENT FUNCTIONS

Dihalogen compounds

When in aliphatic hydrocarbons more than one substituent enters at *different* carbon atoms, the number of possible structural isomers increases rapidly with the length of the chain. Thus, theory predicts six isomeric dichloro-*n*-pentanes, in which the two chlorine atoms are attached to *different* carbon atoms. The possible positions are as follows:



The most easily obtainable are the "*vicinal*" or 1:2-dihalogen-derivatives of the paraffin hydrocarbons. The addition of halogens to olefins (see p. 53) is a convenient method of obtaining these chloro- and bromo-compounds:



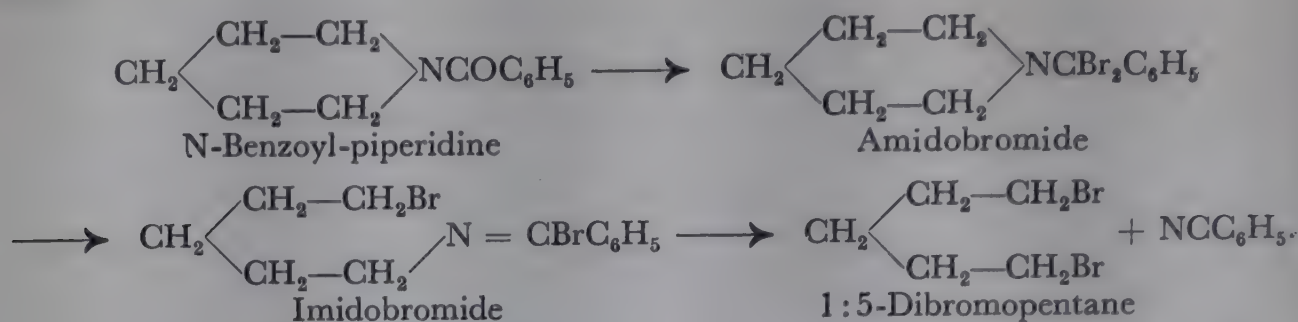
The very unstable vicinal iodine compounds are usually obtained by indirect methods.

Amongst the halogen derivatives in which the halogen atoms are not adjacent, those with *terminal* halogen atoms are of special interest from the preparative point of view. A simple procedure for the preparation of trimethylene bromide, $BrCH_2CH_2CH_2Br$, is the addition of hydrogen bromide to allyl bromide at low temperatures:



New methods have been found by v. Braun for the preparation of 1:4-dibromobutane, and particularly 1:5-dibromopentane. The benzoyl compound of the cyclic amine *piperidine* is heated with phosphorus pentabromide. At first an amido-

bromide is produced, which breaks down into 1:5-dibromopentane and benzonitrile:



The use of phosphorus chlorides gives 1:5-dichloropentane, and analogous reactions with *N*-benzoyl-pyrrolidine, $\begin{array}{c} \text{CH}_2\text{—CH}_2 \\ | \\ \text{CH}_2\text{—CH}_2 \end{array} \text{NCOC}_6\text{H}_5$, give 1:4-dibromo- and 1:4-dichlorobutane.

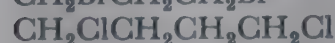
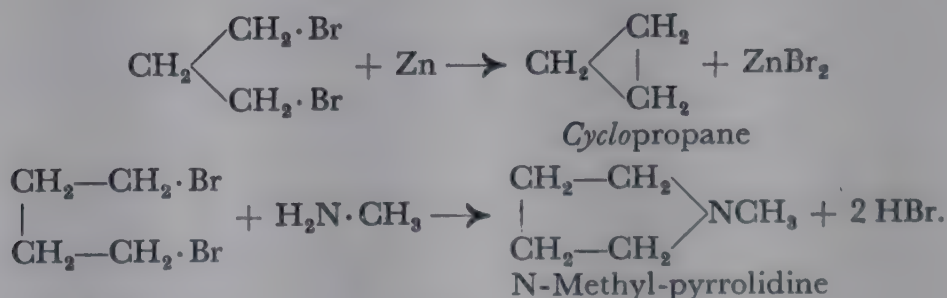
As regards reactivity the saturated dihalogen compounds resemble the alkyl halides in every way. The two halogen atoms can be replaced by many other groups (OH, NH₂, SH, CN, etc.), and in this way different hydrocarbon derivatives with two substituents can be synthesized, e.g.:



Alkalis generally remove hydrogen halide from them, and either one or two molecules are removed according to the temperature and strength of the alkali. The vicinal dihalogen compounds give in this way either unsaturated halogen derivatives, or acetylenic hydrocarbons:



Those derivatives which have the halogen atoms in the 1:3, and more especially in the 1:4, or 1:5 positions, show a pronounced tendency to react with the formation of cyclic compounds. We will often encounter such ring-closure syntheses. The principle of the method may be illustrated by the following formulæ:



Ethylene dichloride, b.p. 84°

Ethylene dibromide, b.p. 132°

Propylene chloride, b.p. 97°

Propylene bromide, b.p. 142°

Trimethylene chloride, b.p. 120°

Trimethylene bromide, b.p. 167°

Tetramethylene chloride, b.p. 162°

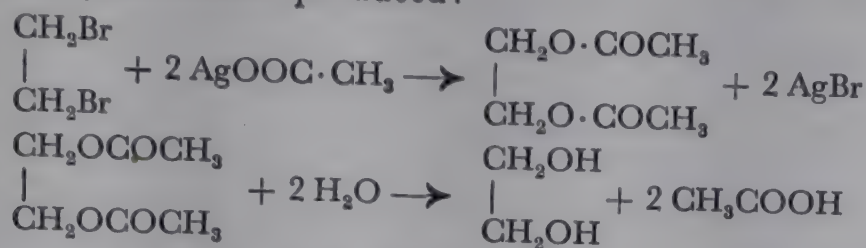
Tetramethylene bromide, b.p. 197°

Pentamethylene chloride, b.p. 178°

Pentamethylene bromide, b.p. 223°

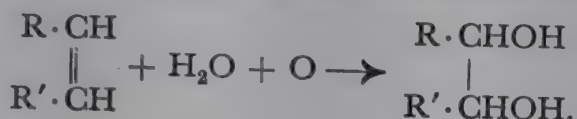
Glycols¹

A good example of the use of the dihalogen compounds in syntheses is the preparation of the dihydric alcohols, or *glycols*. These were discovered by Wurtz, by allowing silver acetate to act upon vicinal dihalogen derivatives, and hydrolysing the glycol acetate produced:

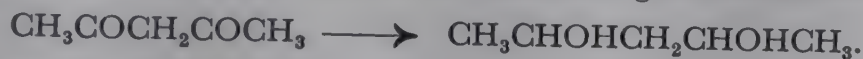


This method is still the most used synthesis of glycol, though, as a rule, the silver acetate is replaced by the cheaper and equally suitable potassium acetate. A direct exchange of the halogen atoms for hydroxyl groups is possible with weak alkalis, e.g. hot sodium carbonate solution, but the yields are usually poor owing to side reactions.

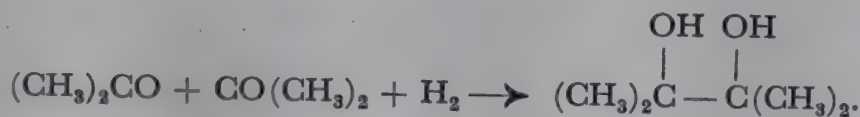
The formation of vicinal glycols from olefins (see p. 55) by careful oxidation with potassium permanganate has already been mentioned:



The reaction often does not run smoothly, and is therefore used, as a rule, only for preparative purposes, when no other methods of obtaining the alcohols concerned are available. The reduction of diketones gives secondary glycols:



Ditertiary glycols have already been met with in the pinacols (see p. 174), which are obtained by suitable reduction of ketones by means of sodium amalgam and water:



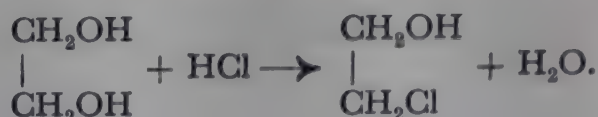
The lower glycols are viscous, clear liquids. The higher ones are crystalline. Some, such as ethylene glycol, $\text{CH}_2\text{OH} \cdot \text{CH}_2\text{OH}$, taste sweet. They are only slightly poisonous to animals, and are not intoxicating, but in man the taking of large doses has been said to lead to serious injuries. They dissolve readily in water, and are different in this respect from the higher monohydric alcohols. It is a general phenomenon that increasing the number of hydroxyl groups makes the compound concerned more soluble in water.

In chemical behaviour the dihydric alcohols naturally show many similarities to the monohydric alcohols. Thus, they form alcoholates, esters, and ethers. Whilst phosphorus pentachloride replaces both hydroxyl groups in ethylene glycol by chlorine:

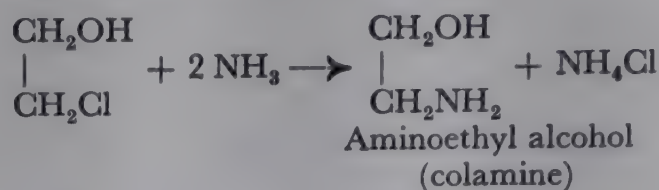


hydrogen chloride reacts with one hydroxyl group more rapidly than with the other. The preparation of *ethylene chlorhydrin* and similar chlorhydrins can be based on this fact:

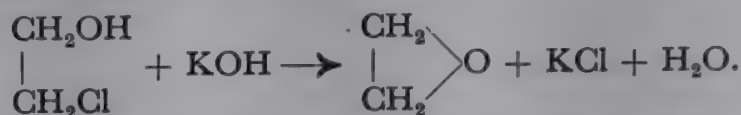
¹ J. W. LAWRIE, *Glycerol and the Glycols*, New York, (1928).



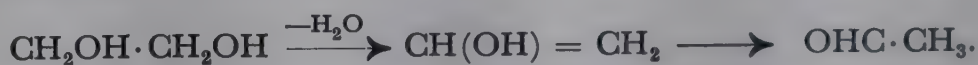
Ethylene chlorhydrin is an important substance, which is suitable for syntheses of various kinds. Thus it is used in the production of novocaine, indigo, and mustard gas, $(\text{ClCH}_2\text{CH}_2)_2\text{S}$. With ammonia and amines, the chlorhydrins form amino-alcohols:



Strong alkalis convert them into *alkylene oxides*.¹

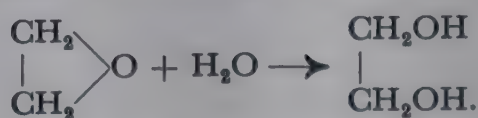


The alkylene oxides are very volatile (ethylene oxide, b.p. 12.5°). They can be regarded as internal anhydrides of the glycols. They cannot usually be prepared by the direct removal of water from the glycols, as the latter are dehydrated in another way when treated with dehydrating agents (zinc chloride, acids). With these, they form aldehydes or ketones, which are produced by the following series of reactions:

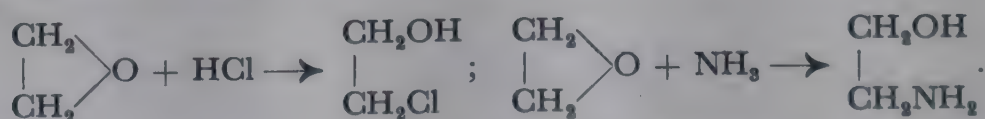


From the course of this process of dehydration it may be concluded that there is a certain resistance to the formation of the alkylene oxides; the reaction takes another course, it takes the path of least resistance. Similar phenomena are often observed when the compounds which it is desired to prepare are very unstable and rich in energy.

That this is the case for the alkylene oxides is proved by their many reactions, into which they enter with great readiness. Even very dilute sulphuric acid is sufficient to break the ethylene oxide ring in the cold, and to regenerate glycol:



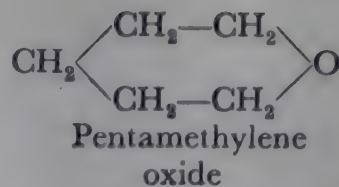
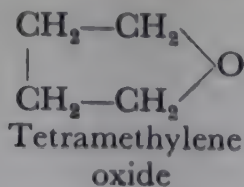
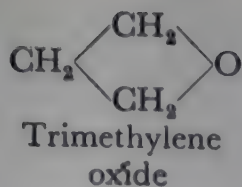
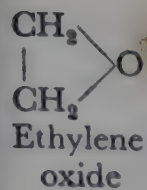
Hydrogen chloride adds on with formation of chlorhydrins, and ammonia produces amino-alcohols:



Their capacity for adding on hydrogen chloride is so great that they precipitate metal hydroxides from solutions of chlorides (MgCl_2 , FeCl_3) by combining with the hydrogen chloride produced from the salt by hydrolysis, thus shifting the equilibrium between the chloride and hydroxide in favour of the latter.

If this reactivity of the alkylene oxides is compared with the properties of their cyclic homologues, *trimethylene oxide*, *tetramethylene oxide*, and *pentamethylene oxide*:

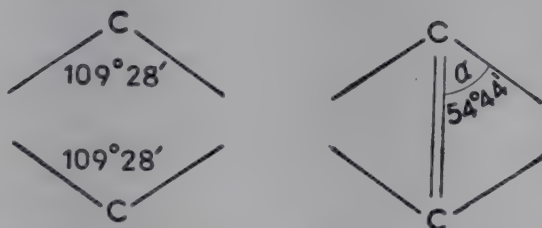
¹ S. BODFORSS, *Die Äthylenoxyde*, Stuttgart, (1920).



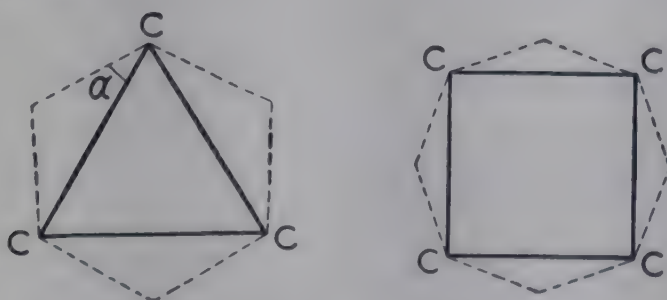
it is seen that not only are the homologues formed with much greater readiness (they are obtained by the elimination of water from the corresponding 1:3-, 1:4-, or 1:5-glycols), but that the re-opening of the ring is much more difficult. Especially is this true of the five- and six-membered heterocyclic rings (tetramethylene oxide, pentamethylene oxide). These facts are special cases of a general phenomenon, which can be expressed in the form that in similarly constructed ring systems the stability always increases from the three-membered to the five-membered ring. Hand in hand with this, the readiness of ring formation increases in the same way. The six-membered heterocyclic ring is also characterized by very great stability, being very little less stable than the five-membered.

The affinity relationships in the molecules of organic compounds thus seems to favour the formation of five- and six-membered rings, and to hinder that of four- and especially three-membered rings. A. v. Baeyer has given an explanation of this, which is known as "*Baeyer's strain theory*". In spite of its rather schematic treatment of our ideas of valency forces, it explains satisfactorily a good deal of the experimental material in this field.

If it is assumed, with Le Bel and van 't Hoff, that the carbon atom is at the centre of a regular tetrahedron, and that the four carbon valencies are directed to the apices of the tetrahedron, the angle between two valency bonds must be $109^{\circ} 28'$. If two carbon atoms are linked together by two valency bonds to form an ethylenic compound, each valency must be bent by an angle $109^{\circ} 28' / 2 = 54^{\circ} 44'$ from its normal position:



For the formation of the three-membered ring the deviation of the valencies from their normal position is $\frac{109^{\circ} 28' - 60^{\circ}}{2} = 24^{\circ} 44'$, for the four-membered ring, $\frac{109^{\circ} 28' - 90^{\circ}}{2} = 9^{\circ} 44'$, for the five-membered ring, $0^{\circ} 44'$, and for the six-membered ring $-5^{\circ} 16'$.



It is now clear, that those rings are the most stable in which the directions

of the carbon valency forces are the least deviated from their natural positions, i.e. the five-membered, and to a lesser extent the six-membered rings. It has been mentioned before that all experimental results agree with this. For the formation of the seven and eight-membered rings the relationships become more complicated, since there the members of the ring need not all lie in one plane. It is therefore possible to construct higher ring systems which are also strainless. Moreover, in six-membered rings the individual members of the ring lie as a rule somewhat out of the planar position.

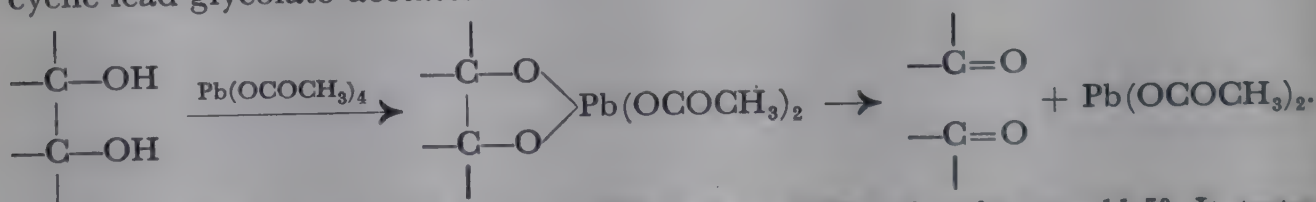
Not only is the strongly unsaturated and energy-rich state of the two-, three-, and four-membered rings indicated by the ease with which the ring is split, but also by the *increments of the molecular refraction* (which has already been shown to be due to the unsaturated state of the molecule, p. 52), and also by the *energy liberated* when various ring systems are opened. The increments in the molecular refraction are given below:

Increments \overline{F}_D	for the double bond	about 1.7
\overline{F}_D	„ „	three-membered ring, about 0.7
\overline{F}_D	„ „	four-membered ring, about 0.46
\overline{F}_D	„ „	five-membered ring, about 0
\overline{F}_D	„ „	eight-membered to the fifteen-membered ring, about -0.55

(These increments vary somewhat for the different derivatives of the hydrocarbons.) The energy liberated when the ring is opened by the addition of two hydrogen atoms is as follows:

Trimethylene ring	37.1 kcal.
Tetramethylene ring	39.9 kcal.
Pentamethylene ring	16.1 kcal.
Hexamethylene ring	14.3 kcal.

Glycols with *adjacent* hydroxyl groups can be smoothly oxidized by certain oxidizing agents, the chain breaking between the carbon atoms bearing the hydroxyl groups, and aldehydes or ketones being produced. Suitable oxidizing agents are periodic acid, recommended by Malaprade, or lead tetraacetate proposed by Criegee. In the latter case the cleavage probably takes place through cyclic lead glycolate-acetates:



ETHYLENE GLYCOL, $CH_2OH \cdot CH_2OH$, boils at 197° and melts at -11.5° . It tastes sweet, and is miscible with water in all proportions. It serves as a substitute for glycerol. For its oxidation products (glycolaldehyde, glycolic acid, glyoxal, glyoxylic acid, oxalic acid) see pp. 255 ff. Glycol dinitrate is an explosive.

The diether of glycol, DIOXANE, $O \begin{array}{c} \diagup CH_2 \cdot CH_2 \\ \diagdown CH_2 \cdot CH_2 \end{array} O$, has attained great importance

in recent years as an excellent solvent. It can be obtained from glycol by heating with some concentrated sulphuric acid. It is a mobile liquid (b.p. 102° , m.p. 11°) and is miscible with water in all proportions. With anhydrous acids and halogens dioxane combines to form addition compounds of the oxonium type.

PROPYLENE GLYCOL, $CH_3CHOHCH_2OH$, b.p. 189° . Optically active forms have been obtained by bacterial resolution, by the degradation of L- β -hydroxybutyric acid, and by synthesis.

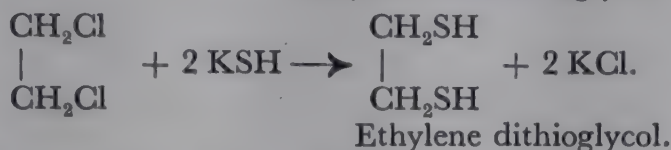
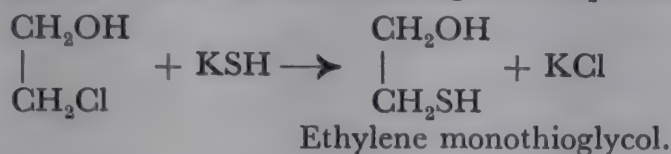
TRIMETHYLENE GLYCOL, $\text{CH}_2\text{OHCH}_2\text{CH}_2\text{OH}$, b.p. 210° . Found in the products of bacterial fermentation of glycerol.

SYMMETRICAL DIMETHYLETHYLENE GLYCOL, $\text{CH}_3\text{CHOHCHOHCH}_3$, is found among the products of fermentation of glucose by the *Bacillus lactis aerogenes*, *l*-2:3-butanediol is formed from corn-mash by the action of *Bacillus polymyxa*.

TETRAMETHYLENE GLYCOL, $\text{CH}_2\text{OH}(\text{CH}_2)_2\text{CH}_2\text{OH}$, b.p. 230° . PENTAMETHYLENE GLYCOL, $\text{CH}_2\text{OH}(\text{CH}_2)_3\text{CH}_2\text{OH}$, b.p. 239° .

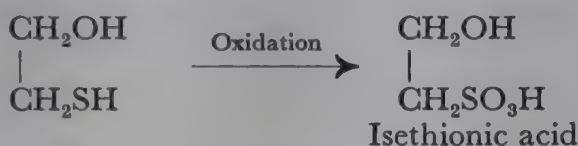
HEXAMETHYLENE GLYCOL, $\text{CH}_2\text{OH}(\text{CH}_2)_4\text{CH}_2\text{OH}$, b.p. 250° .

Mono- and dithioglycols. *Monothioglycols*, $\text{HSCH}_2\cdot\text{CH}_2\text{OH}$, are formed from the halogen hydrins and potassium hydrogen sulphide. *Dithioglycols* are obtained in an analogous way from the dihalogen compounds:

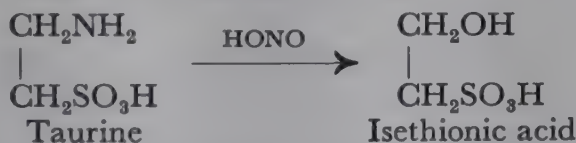


Both classes of compounds have the characteristic properties of the mercaptans. The lower members are colourless oils, which can be distilled.

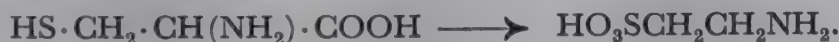
The oxidation product of ethylene monothioglycol, *isethionic acid*, obtainable in several ways, is of interest:



It is also formed by the action of nitrous acid on *taurine*:



Taurine is found combined with cholic acid as *taurocholic acid* in ox-bile. Its parent substance is the sulphur-containing protein amino-acid cysteine, from which it originates by decarboxylation and oxidation:

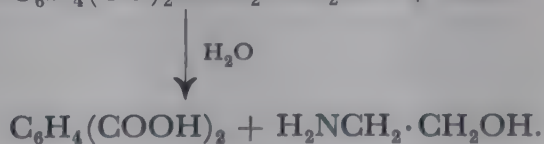
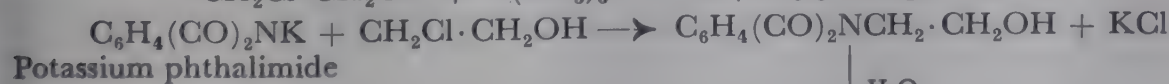


Amino-alcohols

Amongst the *amino-alcohols* (hydroxy-amines) are to be found some physiologically important substances, such as *colamine*, $\text{CH}_2\text{NH}_2\cdot\text{CH}_2\text{OH}$, and *choline*, $\text{HO}(\text{CH}_3)_3\text{N}\cdot\text{CH}_2\cdot\text{CH}_2\text{OH}$. The benzoic acid esters of the amino-alcohols act as anæsthetics, and have therefore become important as substitutes for cocaine.

Amino-alcohols can be prepared:

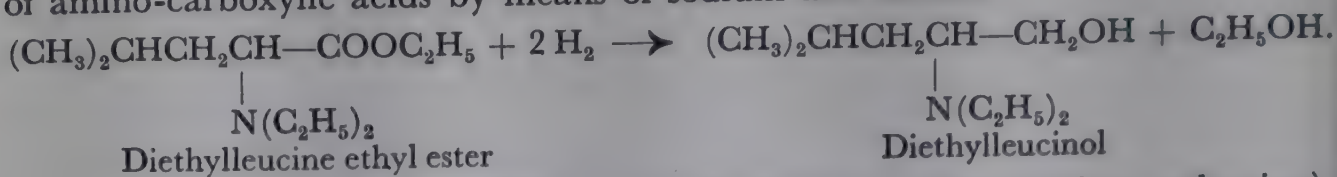
1. From the halogen hydrins and ammonia, or amines, or potassium phthalimide. In the latter case, the reaction must be completed by eliminating the phthalic acid radical by means of strong acids:



2. From alkylene oxides by the action of amines and water, or ammonia:



3. By reduction of amino-aldehydes, amino-ketones, and especially esters of amino-carboxylic acids by means of sodium and alcohol:

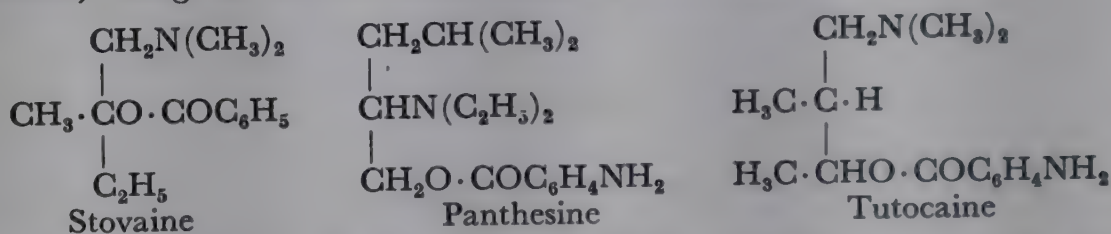


AMINOETHYL ALCOHOL (β -hydroxyethylamine, ethanolamine, colamine), $\text{CH}_2\text{NH}_2\text{CH}_2\text{OH}$, is a viscous, strongly basic oil, soluble in all proportions in water and alcohol, but little soluble in ether. It boils at 171° . It is known to be a product of decomposition of *phosphatides* (see p. 218), and is said to occur, combined with glycerophosphoric acid, chiefly in the kephalin fraction. Its N-monomethyl-, and N-dimethyl-compounds,



have been obtained as decomposition products of morphine and thebaine derivatives.

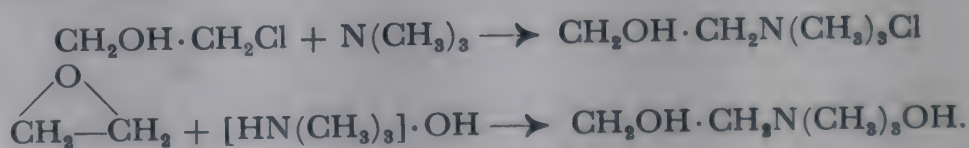
The hydrochloride of the *p*-aminobenzoic ester of N-diethylaminoethyl alcohol, $\text{H}_2\text{N} \cdot \text{C}_6\text{H}_4 \cdot \text{CO} \cdot \text{OCH}_2 \cdot \text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2$, is the much-used local anæsthetic *novocaine*.¹ The cocaine substitutes *stovaine*, *panthesine*, and *tutocaine*, are similarly constituted, being all derived from complex amino-alcohols:



CHOLINE, $\text{CH}_2\text{OH} \cdot \text{CH}_2\text{N}(\text{CH}_3)_3\text{OH}$. Choline is of outstanding biological interest. It is colamine which has been fully methylated at the nitrogen atom. It is the most important basic component of lecithin (see p. 218), and is widely distributed in human and animal organs, as well as in plants. In biological processes, choline acts as a methylating agent; it itself can obtain its methyl groups from methionine (q.v.).

Free choline is very hygroscopic, but can be obtained crystalline. It is a strong base. Many of its salts, e.g. the chloride, $\text{CH}_2\text{OH} \cdot \text{CH}_2\text{N}(\text{CH}_3)_3\text{Cl}$, as well as the picrate, crystallize well.

Choline can be obtained from lecithins, but is usually prepared by synthesis, e.g. from ethylene chlorhydrin and trimethylamine, when choline hydrochloride is obtained, or by the addition of trimethylamine to ethylene oxide, which gives the free choline base:



By processes of decay, or by boiling choline with baryta-water, water is eliminated and the syrupy and very poisonous *neurine* is formed:

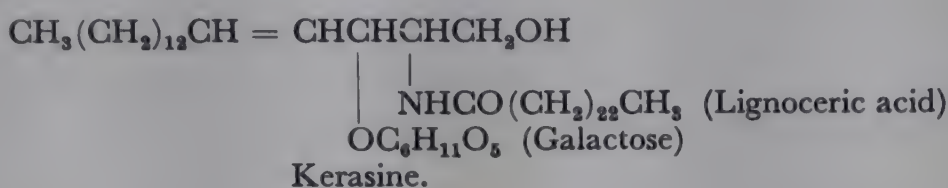
¹ CHARLES F. HADFIELD, *Practical anaesthetics*, 2nd ed. London, (1931).



Choline has a lowering effect on the blood-pressure, frequently followed by a slight increase. It exerts a slightly contracting effect on the uterus.

A much more active substance is its acetyl derivative, acetylcholine. It is contained in ergot and in shepherd's purse (*Capsella bursa pastoris*), in active muscle, in the spleen of cattle and horses, etc. It possesses a powerful muscle-contracting effect, and causes considerable lowering of the blood pressure. A dilution of 1:1000 million is sufficient to renew contractions in the surviving intestines of the guinea-pig. The compound is considered to be a hormone of the peristaltic intestine.

Higher amino-alcohols are often found in animal organs. There is, for example, a choline, $\text{C}_6\text{H}_{17}\text{NO}_2$, in muscle and in extract of crabs. Especially important, however, is SPHINGOSINE, $\text{CH}_3 \cdot (\text{CH}_2)_{12} \cdot \text{CH} = \text{CH} \cdot \text{CHOH} \cdot \text{CHNH}_2 \cdot \text{CH}_2\text{OH}$, which is found in the brain cerebrosides combined with lignoceric acid and galactose as *kerasine*:



The *sphingomyelins* occurring in brain and in organs rich in phosphatides also contain sphingosine, which is here combined with one molecule each of fatty acid, choline, and phosphoric acid.

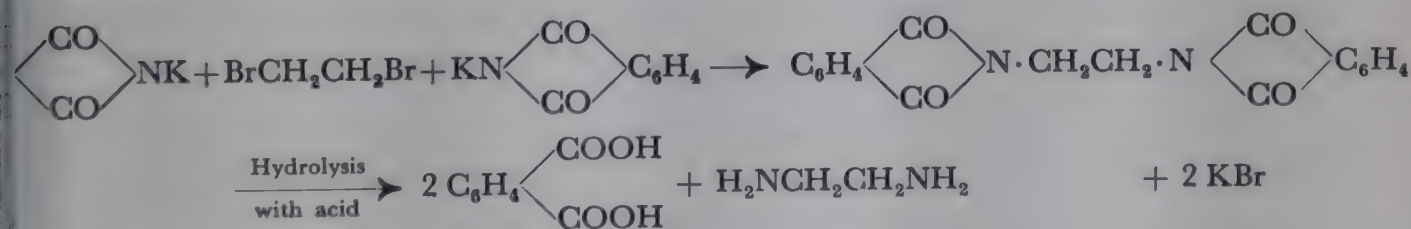
Diamines

Similar methods to those used for obtaining the monoamines, can be used for the preparation of *diamines*. Thus they may be obtained:

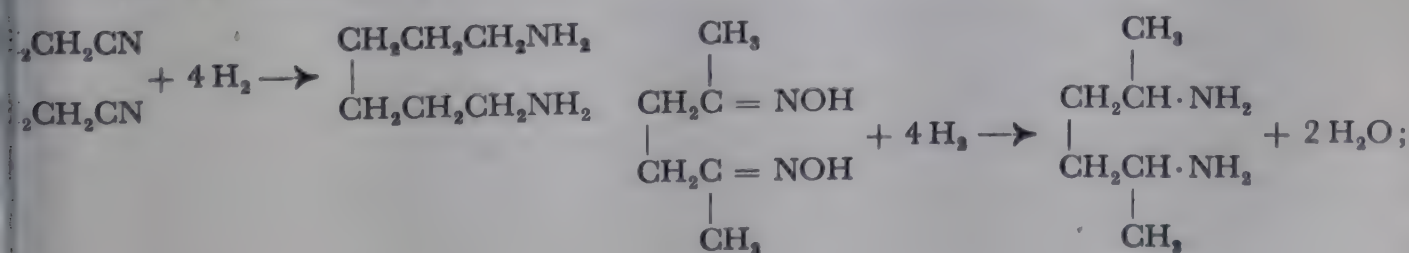
(a) From dihalogen derivatives and ammonia, or amines:



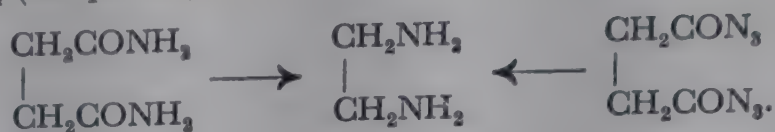
In addition to the primary bases, secondary and tertiary bases are also produced in this reaction. In order to prevent their formation, the phthalimide synthesis of Gabriel can be used:



(b) By reduction of dinitriles, dioximes, and dihydrazones:

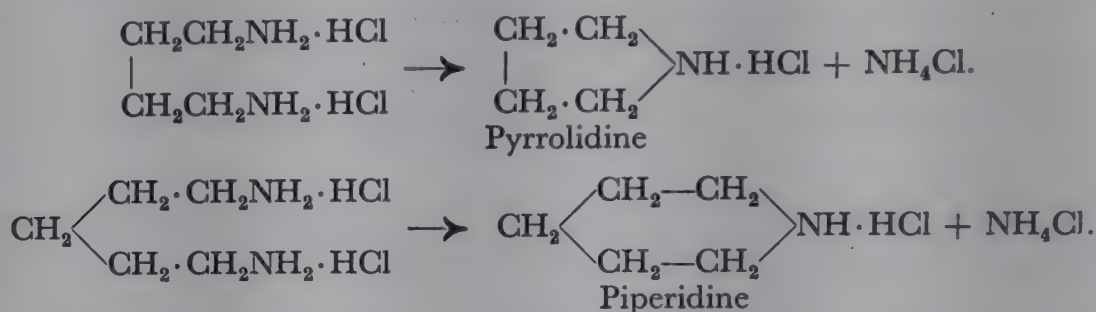


(c) By degradation of the amides or azides of dicarboxylic acids by the methods of A. W. Hofmann and Curtius respectively, or from the amides by means of LiAlH_4 (see p. 130):



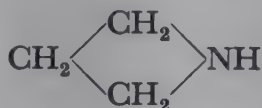
The aliphatic diamines are readily soluble in water, and have a characteristic smell reminiscent of that of the higher monoamines. They fume in air, and are strong bases. The further apart the two amino-groups are in the molecule, the stronger bases they are. They form stable monacid and diacid salts.

Their connection with the cyclic bases is very interesting. If the hydrochlorides of tetramethylenediamine, or pentamethylenediamine are heated in the dry state, the five-membered or six-membered heterocyclic compounds *pyrrolidine* and *piperidine*, respectively, are formed. The latter particularly is formed fairly smoothly:



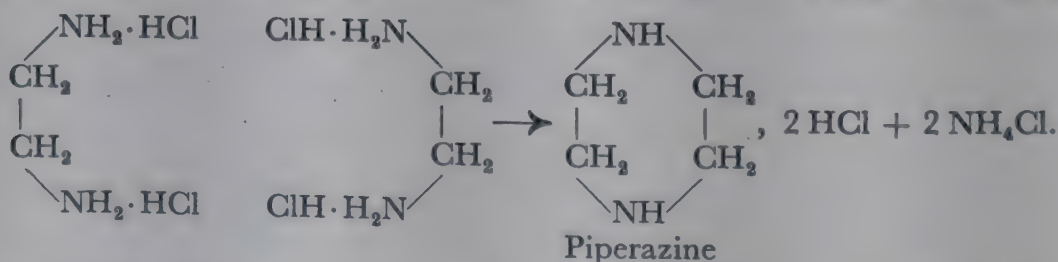
The ease with which five- and six-membered rings are formed is again shown in these reactions.

Trimethylenediamine, $\text{H}_2\text{NCH}_2\text{CH}_2\text{CH}_2\text{NH}_2$, gives under these conditions, only a very small amount of trimethyleneimine:

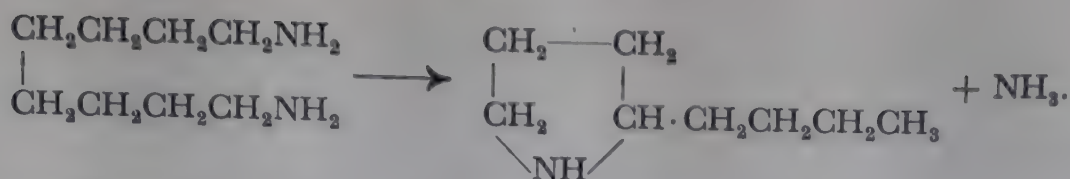


and in the case of ethylenediamine, $\text{H}_2\text{NCH}_2\text{CH}_2\text{NH}_2$, there is no ring

closure at all to give the three-membered ring ethyleneimine, $\text{CH}_2 - \text{CH}_2 - \text{NH}$. Instead of this unstable ring system, the six-membered *piperazine* is formed:



The special position occupied by the five- and six-membered rings with regard to ease of formation is shown even more clearly when the behaviour of the bases in which the two amino-groups are separated by more than five CH_2 -groups is compared with that of the lower diamines. Their hydrochlorides yield on heating not cyclic amines with rings of seven, eight or more members, but five- or six-membered rings. For example, octamethylenediamine gives *n*-butylpyrrolidine, though the mechanism of the reaction is not very clear:



1:6-diamino-*n*-hexane gives α -ethylpyrrolidine.

ETHYLENEDIAMINE, $\text{H}_2\text{NCH}_2\text{CH}_2\text{NH}_2$, is a liquid with an ammoniacal smell. It boils at 116.5° , and melts at 8.5° . TRIMETHYLENEDIAMINE, $\text{H}_2\text{N}(\text{CH}_2)_3\text{NH}_2$, boils at 136° .

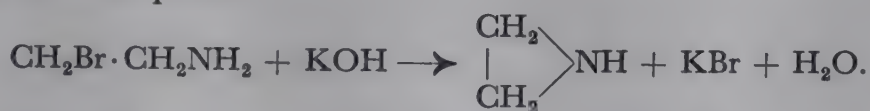
TETRAMETHYLENEDIAMINE, $\text{H}_2\text{N}(\text{CH}_2)_4\text{NH}_2$, or *putrescine*, and PENTAMETHYLENEDIAMINE, $\text{H}_2\text{N}(\text{CH}_2)_5\text{NH}_2$, or *cadaverine*, are of biological importance. Both bases were discovered by Brieger in decaying proteins, and were called "cadaver poisons" or *ptomaines*. The poisonous nature of proteins which are undergoing bacterial decomposition depends not on their ptomaine content, but on poisons of unknown chemical nature, the so-called *toxins*, the formation of which is connected with the bacterial growth.

The parent substances of putrescine and cadaverine are two amino-acids, *arginine*, (see p. 287) and *lysine* (see p. 287) which occur in protein. Arginine is first broken down to ornithine, and this is decarboxylated by bacteria to give putrescine. In the same way, the elimination of carbon dioxide from lysine gives cadaverine (see p. 291).

The ability to produce putrescine and cadaverine is shared by numerous bacilli (including the tetanus and cholera bacilli) and by many moulds. This is the reason why the two bases are so frequently met with in nature. They are found for example in cheese, ergot, fly agaric, brewer's yeast, and in *Hyoscyamus muticus*. In the human disease cystinuria, they are found in considerable quantities in the urine and fæces.

Putrescine boils at $158\text{--}160^\circ$ and melts at $27\text{--}28^\circ$. Cadaverine is a liquid boiling at $178\text{--}179^\circ$.

ETHYLENEIMINE, $\begin{array}{c} \text{NH} \\ \diagup \quad \diagdown \\ \text{CH}_2 \text{---} \text{CH}_2 \end{array}$, the nitrogen analogue of ethylene oxide (see p. 244) can be obtained from bromoethylamine by withdrawal of hydrogen bromide with caustic potash:



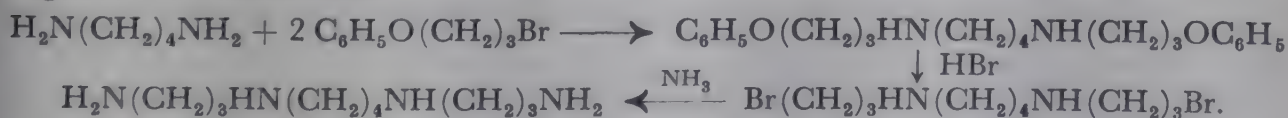
The compound is very reactive, the ring being easily broken. It is a liquid base, with an ammoniacal smell. It boils at 56° .

SPERMINE. Spermine, isolated by Schreiner from fresh human sperm, has recently been synthesized and its constitution elucidated by Dudley. The base is an aliphatic tetramine of the structure:



It has a strong alkaline reaction, is crystalline, and forms well-crystallized salts, some of which are difficultly soluble.

Its synthesis was carried out in the following way which is conclusive as regards its constitution:



In addition to spermine there is in sperm a second polyamine, *spermidine*, of which the structure is also known with certainty from decomposition reactions, and synthesis. It is a triamine, $\text{H}_2\text{N}(\text{CH}_2)_3\text{NH}(\text{CH}_2)_4\text{NH}_2$.

CHAPTER 15. POLYHALOGEN COMPOUNDS. HALOGEN DERIVATIVES OF ALDEHYDES AND CARBOXYLIC ACIDS

I. Polyhalogen derivatives

Acetylene is the starting point for the preparation of various higher chlorinated derivatives of ethane, which are used as solvents and extracting agents.

ACETYLENE TETRACHLORIDE (tetrachlorethane), $\text{CHCl}_2 \cdot \text{CHCl}_2$, is formed by the combination of acetylene and chlorine. Since this method is dangerous and may be accompanied by explosions, special reaction conditions are necessary. For example, acetylene and chlorine are passed into antimony pentachloride. The latter combines with the acetylene to form the double compound, $\text{C}_2\text{H}_2 \cdot \text{SbCl}_5$, which is then decomposed by chlorine to give acetylene tetrachloride and antimony pentachloride (Berthelot and Jungfleisch):



In other processes the antimony pentachloride is replaced by sulphur monochloride to which about 1 per cent of iron powder has been added as a catalyst, or the chlorination is carried out in vessels which contain sand as a solid diluent.

On treating acetylene tetrachloride with lime, TRICHLORETHYLENE, $\text{CHCl} = \text{CCl}_2$, is formed. If chlorine is again added to this, PENTACHLORETHANE, $\text{CHCl}_2 \cdot \text{CCl}_3$, is produced. Hydrogen chloride can again be removed from the latter by means of lime, giving PERCHLORETHYLENE, $\text{CCl}_2 = \text{CCl}_2$. Finally, by addition of chlorine to perchlorethylene, HEXACHLORETHANE OR PERCHLORETHANE, $\text{CCl}_3 \cdot \text{CCl}_3$, is formed. DICHLORETHYLENE, $\text{CHCl} = \text{CHCl}$, should be included in this group of halogenated ethane derivatives. It is prepared technically by the reduction of acetylene tetrachloride with zinc dust and water:



The above-mentioned halogen compounds are used (with the exception of hexachlorethane) as solvents and extracting agents for fats, oils, resins, lacquers, and rubber. They have the advantage over petrol in possessing a constant boiling point, and being non-inflammable. Trichlorethylene and dichlorethylene are especially important, since they boil at low temperatures, and do not attack metals even when heated or in the presence of water.

		b.p.
Dichlorethylene	$\text{CHCl} = \text{CHCl}$	55°
Trichlorethylene	$\text{CHCl} = \text{CCl}_2$	87°
Tetrachlorethylene	$\text{CCl}_2 = \text{CCl}_2$	121°
Acetylene tetrachloride	$\text{CHCl}_2 \cdot \text{CHCl}_2$	146°
Pentachlorethane	$\text{CHCl}_2 \cdot \text{CCl}_3$	161°
Hexachlorethane	$\text{CCl}_3 \cdot \text{CCl}_3$	185° (sublimes)

Hexachlorethane smells like camphor, and is used as a substitute for it, and in the manufacture of explosives. Tetrachlorethane is a solvent for cellulose acetate; trichlorethylene is used in syntheses. For example, on heating with alkalis it gives glycolic acid.

II. Halogen derivatives of the aldehydes and carboxylic acids

Chloral. The most interesting and from the practical point of view the most important of the chlorinated aldehydes is *chloral*, CCl_3CHO . To prepare it, chlorine is allowed to act upon alcohol (Liebig). Acetaldehyde is first formed and is gradually chlorinated until chloral is produced, which remains combined

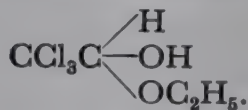
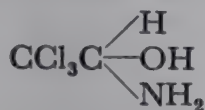
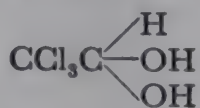
with a molecule of alcohol as chloral alcoholate $\text{CCl}_3\text{C} \begin{array}{l} \text{H} \\ \diagup \\ \text{OH} \\ \diagdown \\ \text{OC}_2\text{H}_5 \end{array}$. The alcohol is then split off by treating the substance with concentrated sulphuric acid.

Chloral is a viscous liquid with an intense smell. It boils at $97-98^\circ$, and solidifies when strongly cooled. It melts at -57.5° .

Being an aldehyde, chloral reduces ammoniacal silver nitrate solution, and turns fuchsin-sulphurous acid (Schiff's reagent) red. It is very easily attacked by alkalis, being converted into chloroform and formic acid:



By the action of small quantities of concentrated sulphuric acid, trimethylamine, or aluminium chloride, chloral is converted into various solid, polymeric modifications (e.g. metachloral). Its behaviour towards water, ammonia, and alcohol is very remarkable. It combines with these substances almost instantaneously to give solid, well-crystallized compounds, which are to be regarded as *chloral hydrate* (m.p. 57°), *chloral ammonia*, and *chloral alcoholate* (m.p. 46°):



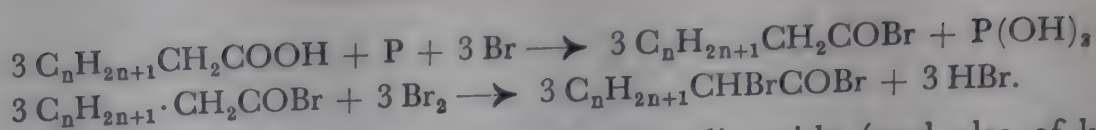
In contrast to the hydrates and ammonias of the simple aldehydes, these compounds are stable. The existence of two hydroxyl groups (or OH and NH_2) attached to the same carbon atom is obviously favoured by the accumulation of the negative substituents (chlorine) at the adjacent carbon atom.

Liebreich introduced chloral into medicine, where it soon acquired considerable use as a hypnotic. In spite of certain after-effects, it has not been completely replaced by the modern hypnotics (veronal and sulphonal preparations), since it is also effective as a stimulant. It is reduced in the organism to trichlorethyl alcohol, which combines with an acid related to glucose, glucuronic acid, $\text{CHO}(\text{CHOH})_4\text{COOH}$, to give *urochloralic acid*,

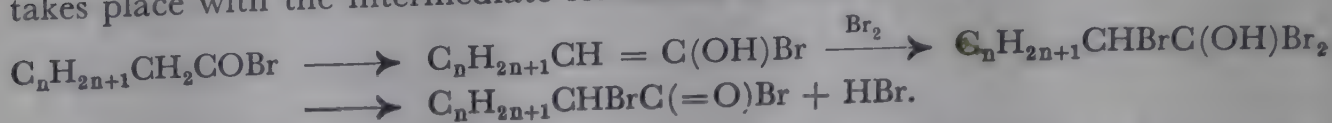


and is excreted as such.

Halogen-substituted fatty acids. The introduction of chlorine and bromine into fatty acids does not take place very smoothly, but can be facilitated by light, halogen carriers (phosphorus, sulphur, etc.), and increase of temperature. The chlorination and bromination of the acid anhydrides and acid halides takes place much more rapidly. In the hands of Hell, Volhard, and Zelinsky, this method has become an exceedingly important preparative process for the halogen-substituted acids. Usually the acid bromide synthesis is combined with the introduction of the halogen into the chain, by acting on the carboxylic acid with bromine and phosphorus simultaneously. The following processes take place:



It is possible that the halogenation of carboxylic acids (and also of ketones) takes place with the intermediate formation of enol forms:



On treatment with water, the α -bromo-fatty acid bromide is decomposed to give the α -bromo-fatty acid. Experience shows that the halogen always enters in the α -position to the carboxyl group, and all hydrogen atoms in the α -position can be successively replaced by chlorine or bromine. The iodo-fatty acids are prepared by the action of potassium iodide on the chloro- or bromo-compounds.

Halogen-substituted fatty acids may also be obtained from hydroxy-carboxylic acids by esterification with halogen hydracids, or by the action of phosphorus halides:

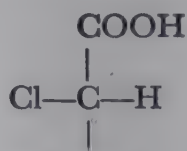


It is often necessary to convert amino-fatty acids into halogen-substituted acids. Nitrosyl chloride and bromide are suitable reagents for this purpose, particularly if they are used in the nascent form as a mixture of nitric oxide and chlorine or bromine:



The great mobility of the halogen in the halogen-substituted carboxylic acids is the basis of their outstanding importance in synthetic work. Just as the alkyl halides are the starting materials in the preparation of numerous other functions, a great variety of ways leads from the halogenocarboxylic acids to other derivatives of carboxylic acids.

As regards the configuration of the optically active α -chlorocarboxylic acids, we now know that the *laevorotatory* forms of α -chloropropionic acid, monochlorosuccinic acid, and dichlorosuccinic acid, correspond to the configuration of natural L-malic acid and the natural protein amino-acids (see p. 285ff.), thus containing the grouping:



MONOCHLORACETIC ACID, $\text{ClCH}_2\cdot\text{COOH}$, is prepared by chlorinating glacial acetic acid in the presence of phosphorus or sulphur. It is used extensively in industry, especially for the synthesis of indigo. It melts at 61° , and boils at 189° . It dissolves readily in water. The solution reacts much more strongly acid, than that of acetic acid. It is a general fact that the dissociation of carboxylic acids is increased by the introduction of halogens, and with the number of halogen atoms introduced.

DICHLORACETIC ACID, CHCl_2COOH , is a liquid boiling at 194° .

TRICHLORACETIC ACID, CCl_3COOH , is prepared by the oxidation of chloral (see p. 253). It is a very strong acid. Alkalis decompose it owing to the accumulation of chlorine at the carbon atom adjacent to the carboxyl group (cf. also chloral):



The corrosive action of trichloroacetic acid is made use of in medicine.

HALOGEN DERIVATIVES OF HIGHER CARBOXYLIC ACIDS. Many of these have been prepared, partly for preparative purposes, but chiefly for the elucidation of stereochemical problems (cf. the Walden inversion). In the majority of cases it is the α -halogen-substituted

carboxylic acids that have been prepared. As regards their chemical properties they are, in general, similar to the chloracetic acids.

The calcium salt of dibromobehenic acid, $(C_{22}H_{41}Br_2O_2)_2Ca$, and that of mono-iodobehenic acid, $(C_{22}H_{43}IO_2)_2Ca$, are used under the tradenames of sabromin and saiodin as bromine and iodine preparations. Iodostarin is diiodotariric acid, $CH_3(CH_2)_{10}CI=CI(CH_2)_4COOH$.

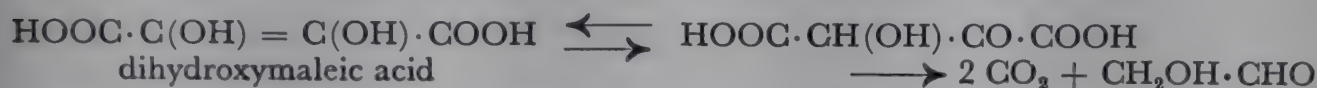
CHAPTER 16. OXIDATION PRODUCTS OF GLYCOL

Hydroxyaldehydes. Hydroxyketones

GLYCOLALDEHYDE, $CH_2OH \cdot CHO$. This is the simplest and most interesting of the monohydroxy-aldehydes. It is formed from glycol (see p. 246) by oxidation with hydrogen peroxide in the presence of ferrous compounds (Fenton):



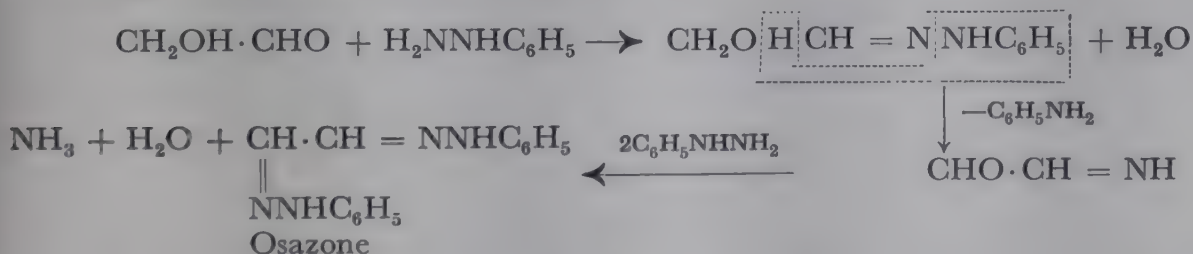
A particularly suitable reaction for the preparation of the substance is the elimination of carbon dioxide from dihydroxymaleic acid (Fenton), which is itself obtained by the oxidation of tartaric acid:



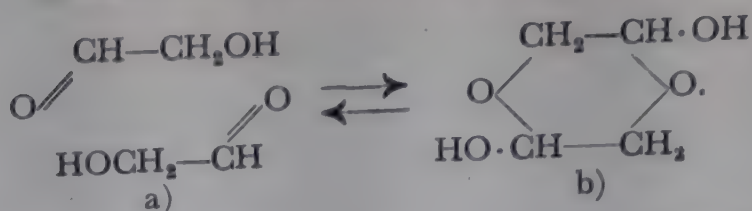
Equally suitable is the ozonolysis of allyl alcohol or cinnamyl alcohol. Glycol-aldehyde may be regarded as the simplest aldehydic sugar ("aldose"), and the formation of carbohydrates from formaldehyde in plants probably takes through it as an intermediate. In this connection it is of interest to note that it can be detected as an intermediate product in the condensation of formaldehyde to sugars, which takes place *in vitro* in the presence of calcium carbonate (H. and A. Euler):



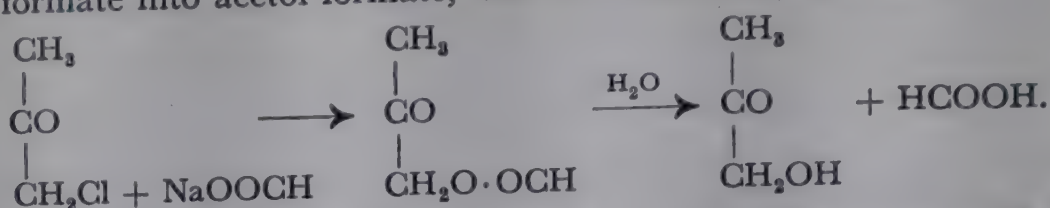
Compounds which contain the group $—CH(OH)CHO$, such as glycol-aldehyde, its homologues and the aldose sugars, are reducing agents and precipitate cuprous oxide from Fehling's solution. Another characteristic reaction which they give is the formation of so-called *phenylosazones* when heated with phenylhydrazine. These compounds are yellow in colour, and are often difficultly soluble, and crystallize well. They are therefore important in the isolation and characterization of hydroxyaldehydes. Their formation takes place through the following intermediate stages (cf. p. 326):



Glycolaldehyde tastes sweet, and is a crystalline substance, readily soluble in water. Shortly after its dissolution in water it is present in the solution in the dimeric state as a *cyclo*-acetal (formula b). It is, however, gradually reconverted into the simple compound (a), as is shown by cryoscopic determinations of its molecular weight:



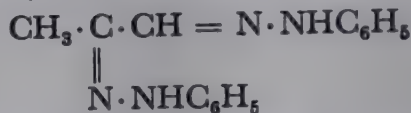
Acetol, $\text{CH}_3\text{COCH}_2\text{OH}$. Acetol is the simplest possible *hydroxyketone*, or *ketol*. It can be prepared from chloracetone, which is first converted by means of sodium formate into acetol formate, and the latter is hydrolysed:



The formation of acetol from propylene glycol by the action of the sorbose bacterium, which has the power, in general, of oxidizing *secondary* (not primary) alcohol groups, is interesting:

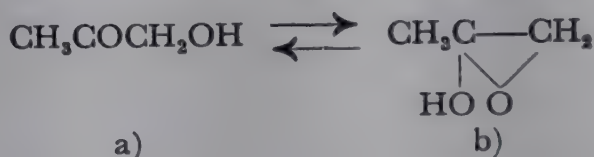


α -Hydroxyketones, like α -hydroxyaldehydes, reduce Fehling's solution quickly, and form osazones with phenylhydrazine. The phenylosazone of acetol has the formula:

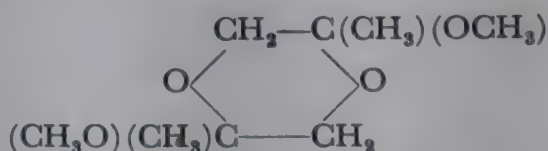


Acetol tastes sweet and burning. It is a liquid which boils at 54° under 18 mm pressure, and is miscible with water.

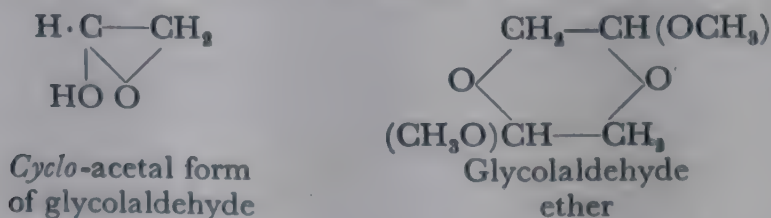
The formula $\text{CH}_3\text{COCH}_2\text{OH}$ does not completely give the constitution of acetol. The tautomeric formula (b) must also be taken into consideration:



and probably the majority of the molecules in the liquid substance are of the latter type, which can be called the *cyclo-acetal form*. Similarly, the dimeric acetol ethers, probably are to be formulated as follows:



The glycolaldehyde mentioned above can also react in the *cyclo-acetal form*, and its alkyl ethers are derived in a similar way from this form:



The tendency to isomerize into cyclic hemiacetals, is a feature of all hydroxyaldehydes and hydroxyketones in which the hydroxyl and carbonyl groups are not too far apart. This property is particularly well-marked in the true sugars (see p. 323) which probably always occur as cyclic hemiacetals.

DIMETHYLKETOL, or acetoin, $\text{CH}_3 \cdot \text{CO} \cdot \text{CHOH} \cdot \text{CH}_3$, is obtained by the reduction of diacetyl:



and is formed in the bacterial fermentation of sugar (e.g. *Bac. tartricus*). It is also present in wine. It boils at 144° .

Acetoin exists in two well-crystallized, dimeric forms, which on distillation, fusion, or even on dissolution, are reconverted into the monomolecular compound. Dirscherl has shown spectroscopically that the combination of the two acetoin groups in the dimeric molecules must take place through subsidiary valencies, since the dimeric forms still possess the absorption bands of the $\text{C}=\text{O}$ -groups. The latter have thus not been saturated by the dimerization.

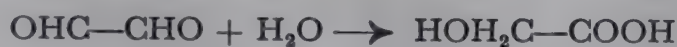
Dialdehydes. Diketones

GLYOXAL, $\text{CHO} \cdot \text{CHO}$, the simplest dialdehyde, is prepared from glycol, ethyl alcohol, or acetaldehyde by oxidation with nitric acid. It may also be obtained by the oxidation of acetylene, or by hydrolysing acetylene tetrachloride by means of 65% sulphuric acid (Wohl). It is always obtained by these methods as a polymeric modification (*polyglyoxal*), which on distillation, breaks down into the monomolecular form, a green, pungent-smelling gas. On cooling this, yellow crystals are obtained, which, however, very soon polymerize into a form of unknown molecular weight. The tendency to polymerize is characteristic of all dialdehydes of the aliphatic series.

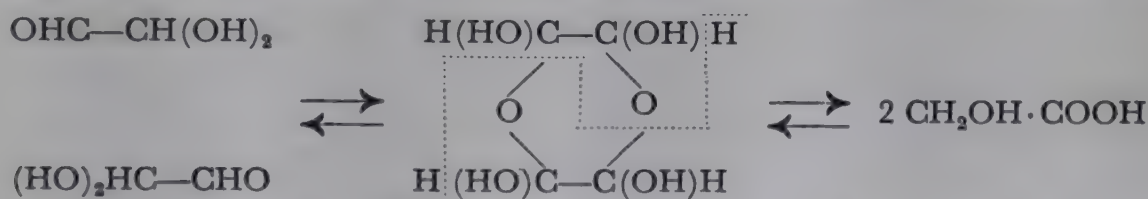
As a dialdehyde, glyoxal gives a dihydrazone with phenylhydrazine:



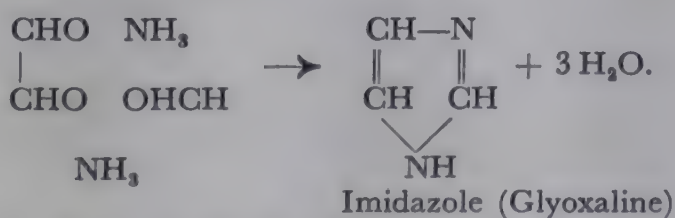
In alkaline solution glyoxal undergoes an intramolecular Cannizzaro reaction, being converted into glycolic acid:



This transformation probably occurs with the intermediate formation of a dimeric hemiacetal form of glyoxal, which then undergoes a double hemiacetal fission:

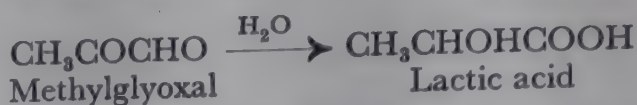


If the dialdehyde is allowed to react with ammonia and formaldehyde, condensation takes place and a heterocyclic compound is formed, known as *imidazole* or *glyoxaline*, various derivatives of which occur in nature and form components of proteins and alkaloids:



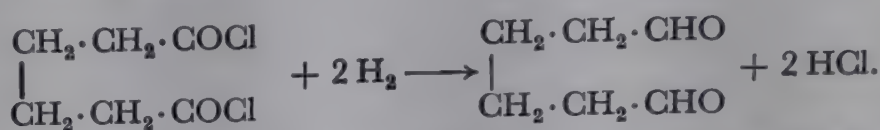
METHYLGLYOXAL, CH_3COCHO . This compound was formerly regarded as an intermediate product in the alcoholic fermentation (see p. 89) of sugars, and in glycogenolysis. To-day this view is no longer held, but it is not excluded that small

quantities of methylglyoxal may be formed in processes of metabolism. On treatment with alkalis or animal and plant enzymes, it is easily converted into lactic acid, by undergoing an intramolecular Cannizzaro reaction (Dakin and Dudley, Neuberg):

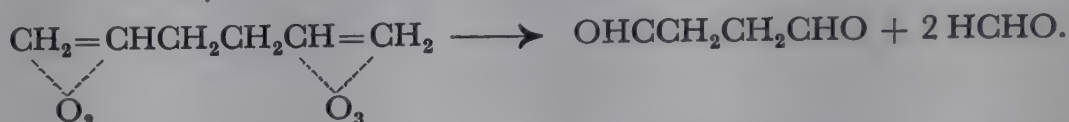


The compound can be prepared by acid hydrolysis of isonitrosoacetone, $\text{CH}_3\text{COCH}=\text{NOH}$, by the oxidation of acetol (see p. 256), and in various other ways.

A fairly general method of preparation of the HIGHER ALIPHATIC DIALDEHYDES is the reduction of the chlorides of the dicarboxylic acids with hydrogen and palladium (in boiling xylene):



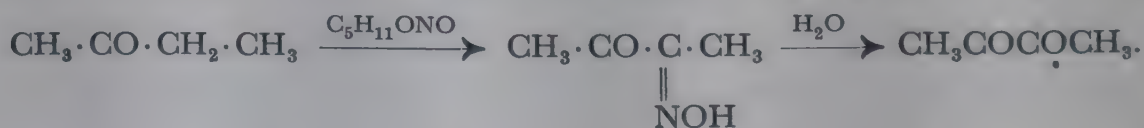
Some of them can be obtained by special methods, e.g. the dialdehyde of succinic acid (SUCCINIC DIALDEHYDE) $\text{OHCCH}_2\text{CH}_2\text{CHO}$, which is obtained by the decomposition of diallyl ozonide with water:



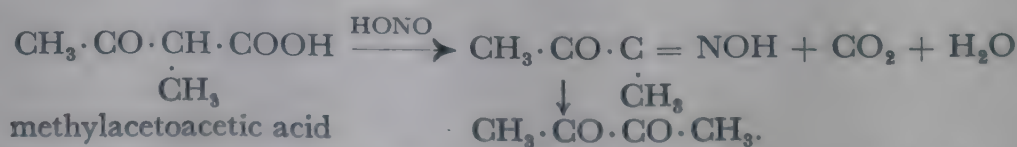
Succinic dialdehyde, and the higher homologues show, like glyoxal, an extraordinary tendency to polymerize, and are very little stable in the monomolecular state. Succinic dialdehyde has become of great interest, as it was used by Robinson as the starting point of syntheses of alkaloids (tropine, cocaine).

Diketones. The diketones are called α -, β -, or γ -diketones, etc. according as the carbonyl groups lie in the 1:2-, 1:3-, or 1:4-positions. These different classes of diketones show many differences and peculiarities in their chemical behaviour.

DIACETYL, $\text{CH}_3\text{COCOCH}_3$, the simplest α -diketone, can be obtained from methyl ethyl ketone or methylacetoacetic ester. In the first case, methyl ethyl ketone is converted into the isonitroso-compound by means of amyl nitrite, and the isonitroso-ketone produced is hydrolysed by acids (H_2SO_4 or HNO_2) (Claisen):



If methylacetoacetic ester is the starting point, it is carefully hydrolysed, and the acid produced is treated with nitrous acid. Carbon dioxide is thus eliminated, the nitrous acid radical is taken up, and the isonitroso-ketone is formed, the same compound as is obtained from methyl ethyl ketone:

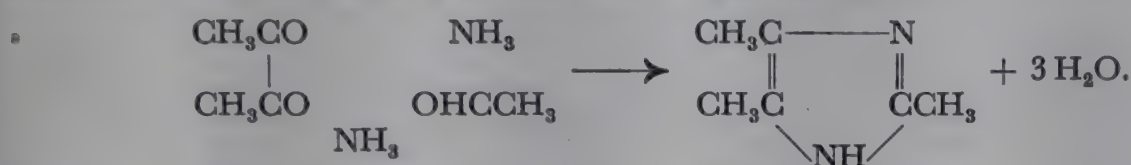


Diacetyl is contained in small quantities in various essential oils (e.g. those from cloves, caraway, etc.). It is also found in butter, of which it forms the

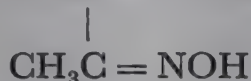
odoriferous matter. Like all α -diketones it is yellow. Already in glyoxal, which also contains two neighbouring CO groups, we have encountered a coloured (green) substance. Colour, i.e. selective absorption of light, is a general property of unsaturated substances. Very often, however, they absorb only in the ultra-violet, so that they appear colourless to our eyes. It is known, however, that with those substances which contain a number of unsaturated groups, the absorption is often displaced into the visible part of the spectrum, and is therefore visible to us. This is, for instance, the case for the α -diketones. The relative position of the unsaturated linkages exerts a significant influence on the colour. Thus, on increasing the distance between the two C=O groups, colourless substances are produced. Most β - and γ -diketones are colourless.

According to a proposal of Witt, groups of atoms which endow a compound with colour are called *chromophores*. All chromophores are unsaturated.

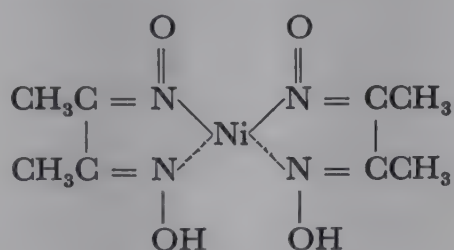
Diacetyl boils at 88° , and shows all the reactions of a ketone. It can (like all other α -diketones) condense with ammonia or amines and aldehydes to give imidazole derivatives, in a similar way to glyoxal (q.v.):



Its dioxime, "dimethylglyoxime", $\text{CH}_3\text{C}=\text{NOH}$, gives coloured complex salts with



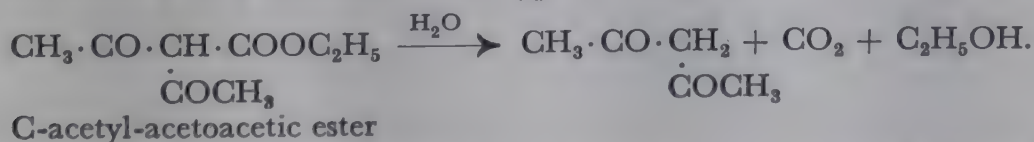
metals. The red nickel salt is specially characteristic and is insoluble; it is often used for the quantitative estimation of nickel:



ACETYLACETONE, $\text{CH}_3\text{COCH}_2\text{COCH}_3$. The condensation of esters of carboxylic acids with ketones, using sodium ethylate, sodamide, or sodium as condensing agent gives rise to β -diketones:



β -Diketones can also be readily obtained by hydrolysis of the easily accessible C-acyl derivatives of acetoacetic ester (q.v.) with water:

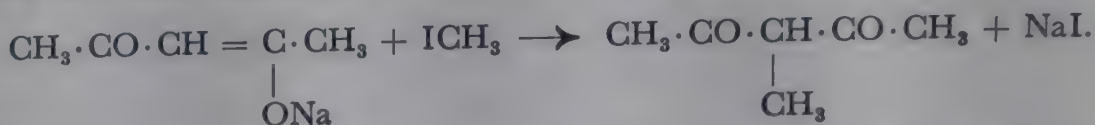


β -Diketones are colourless liquids with a not unpleasant smell. Acetylacetone boils at 139° .

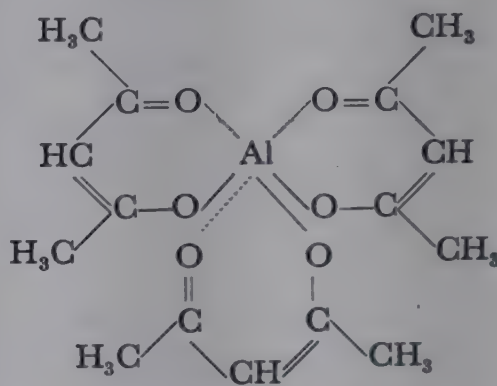
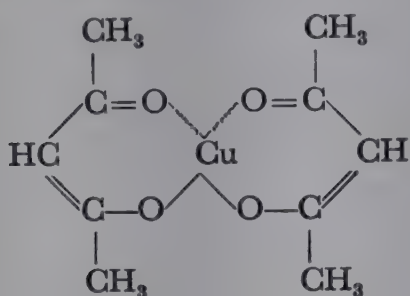
The hydrogen atoms of the methylene group enclosed on each side by carbonyl groups are mobile ("acid methylene groups") and can easily migrate to the adjacent oxygen. The acid enol form is thus produced, which is in equilibrium with the carbonyl (keto) form, and is capable of forming salts.



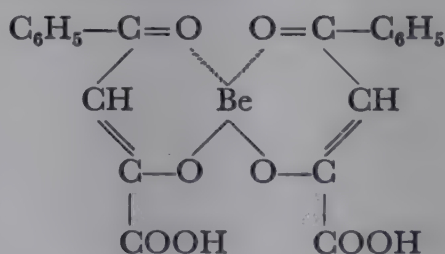
Acetylacetone contains 76.4 per cent of the enol form. The sodium and potassium salts are often used for synthetic purposes. They react with alkyl halides with the formation of C-alkyl derivatives. The reaction products are homologous β -diketones:



Several complex metal salts derived from acetylacetone have characteristic properties, such as the blue copper compounds, soluble in chloroform, the intense red-coloured iron salts, the volatile acetylacetonates of aluminium (b.p. 314°) and beryllium (b.p. 270°), which can both be distilled without decomposition. Their constitutions are represented, according to Werner's coordination theory, by the following formulæ:

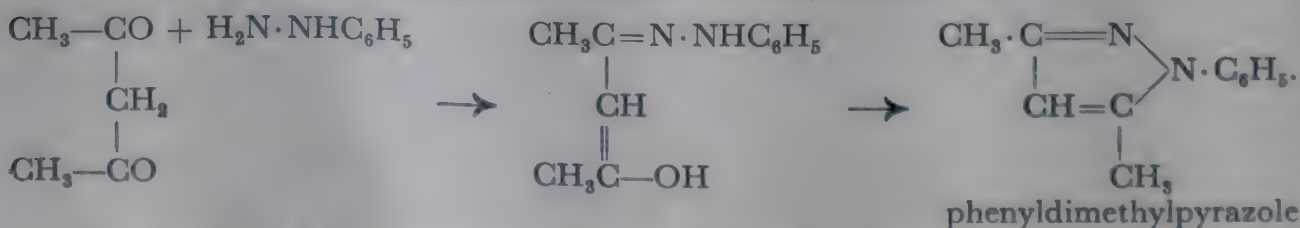


The proof of the accuracy of these formulæ was supplied by Mills and Gotts, who succeeded in resolving a beryllium complex salt of this type (the beryllium compound of benzoylpyruvic acid):



into its optical isomerides. Mirror-image isomerism is only possible in this case if the two diketone residues occupy four coordination positions of beryllium, as in the above formula, and if their arrangement round the central atom is tetrahedral.

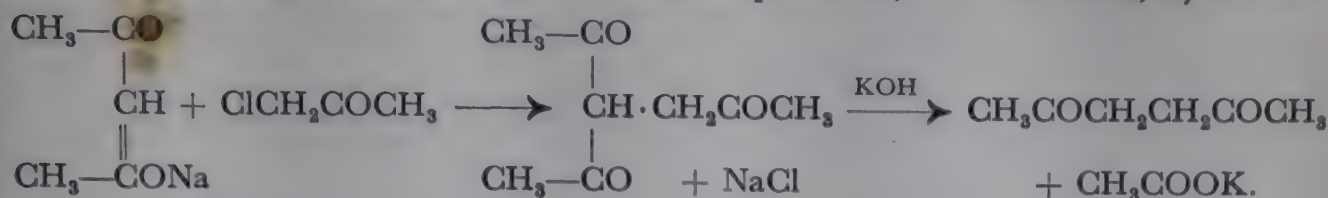
The position of the two carbonyl groups in the β -diketones causes heterocyclic compounds to be produced when they react with various reagents for the carbonyl group, such as phenylhydrazine, hydroxylamine, etc.:



Finally, the β -diketones in general break down when heated with alkalis into acids and ketones:



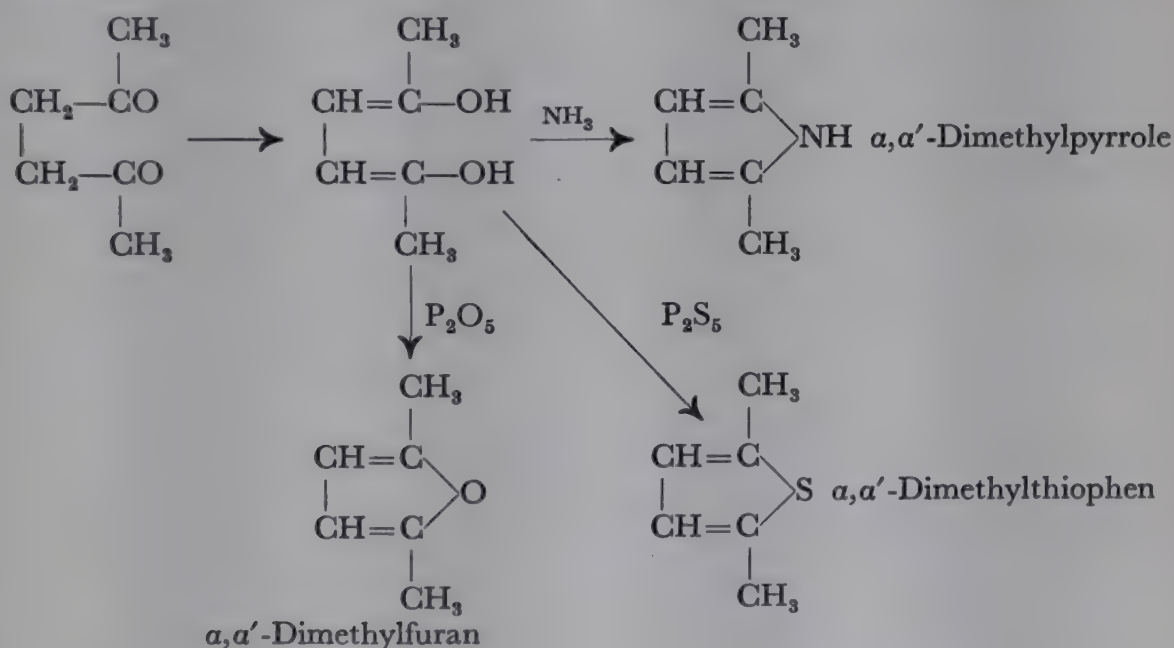
ACETONYLACETONE, $\text{CH}_3\text{COCH}_2\text{CH}_2\text{COCH}_3$. A general method of obtaining γ -diketones depends upon the condensation of sodium acetylacetone with α -chloro-ketones, and the hydrolysis of the reaction products, the triketones, by alkalis:



Acetonylacetone is usually prepared by heating diacetylsuccinic acid:



This simplest γ -diketone is colourless, has an aromatic smell, boils at 191° and melts at -9° . Quite the most remarkable property of acetonylacetone and its analogues is the ease with which they form five-membered heterocyclic rings. This depends on their power to react in the di-enolic form. Thus, acetonylacetone gives α, α' -dimethylpyrrole with ammonia, α, α' -dimethylthiophen with phosphorus sulphide, and is dehydrated by dehydrating agents (P_2O_5 , ZnCl_2) to α, α' -dimethylfuran:



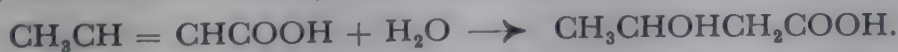
Monohydroxycarboxylic acids

There are two principal methods which are of general use for the preparation of monohydroxycarboxylic acids.

(a) Replacement of halogen in the halogen-substituted fatty acids by heating with water or, sometimes, alkalis:



(b) Addition of water to unsaturated carboxylic acids (see p. 206) by heating with alkalis, and in other cases, with sulphuric acid:



GLYCOLIC ACID, $\text{CH}_2\text{OH} \cdot \text{COOH}$. This substance occurs occasionally in

plants (beet-root, grapes). It is obtained by prolonged heating of an aqueous solution of potassium chloroacetate:



or, technically, from oxalic acid by electrolytic reduction, using lead electrodes.

It forms colourless crystals, and is readily soluble in water; m.p. 80° . Various

anhydrides of glycolic acid are known, e.g. *glycolide*, $\begin{array}{c} \text{CH}_2-\text{O}-\text{CO} \\ | \qquad \qquad | \\ \text{CO}-\text{O}-\text{CH}_2 \end{array}$, and

diglycolic acid, with the ether-like structure, $\begin{array}{c} \text{CH}_2-\text{COOH} \\ \diagup \quad \diagdown \\ \text{O} \\ \diagdown \quad \diagup \\ \text{CH}_2-\text{COOH} \end{array}$.

Glycolic acid has recently been used in cloth-printing.

LACTIC ACID, $\text{CH}_3\text{CHOHCOOH}$. Only α -hydroxypropionic acid, or *ethylidene lactic acid*, occurs in nature; β -hydroxypropionic acid (*ethylene lactic acid*) can be prepared synthetically.

Ordinary lactic acid (α -hydroxypropionic acid) has an asymmetric carbon atom and therefore can exist as the racemate and in optically active forms. It was discovered by Scheele as a constituent of sour milk.

There is a large number of bacteria which can convert sugar into lactic acid. As Buchner showed, these contain an enzyme, lactacidase, which brings about the transformation of the carbohydrate. According to the nature of the micro-organism and the sugar, the racemic, or one of the two active forms is thus produced.

DL-Lactic acid, and lævorotatory lactic acid are produced from glucose, cane-sugar, and maltose (not lactose) by *Bacillus Delbrücki*. This process is used at present for the commercial production of lactic acid. The temperature used is 50° . Some powdered chalk is added to the fermenting liquid to neutralize the acid as it is formed, as otherwise the bacterial growth would be checked by the acid, and would finally be brought to a standstill. The sugar of sweet whey, lactose, is converted into lactic acid by other bacilli, e.g. *B. lactis acidii*.

The occurrence of lactic acid (sarcoplactic acid) in muscle is very important. It is formed from glycogen (see p. 360) by the following series of reactions: glycogen \rightarrow hexose diphosphate \rightarrow triose phosphate \rightarrow phosphoglyceric acid \rightarrow pyruvic acid and the last on reduction gives lactic acid (Embden, see p. 360).

The lactic acid content of muscle increases with muscular activity. Only part of the lactic acid formed, however, is eliminated (Meyerhof).

The occurrence of lactic acid in numerous foodstuffs is to be ascribed to bacterial decomposition of carbohydrates. Thus, it is found in sour milk, wine, sauerkraut, beet leaves, cucumbers, and cheese. Amongst the purely chemical methods of preparation are the replacement of the chlorine in α -chloropropionic acid hydroxyl by means of water or silver oxide, but more particularly the decomposition of sugars (glucose, fructose, etc.) by means of alkalis. Up to 60 per cent of lactic acid can thus be produced.

Pure DL-lactic acid is a clear, viscous liquid. It readily dissolves in water. Its boiling point is 122° (14 mm). When perfectly pure it crystallizes and melts at 18° .

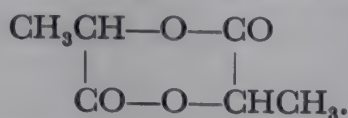
The optically active forms melt at 26° . The extent of their rotation depends on the concentration. For a 10 per cent. solution, $[\alpha]_D = 3.8^\circ$. The L(+)-lactic acid rotates the plane of polarization to the right, the D(−)-lactic acid to the left. On the other hand, all the salts and esters of L(+)-lactic acid are lævorotatory. For their configuration, see p. 302.

The L(+)-lactic acid (sarcolactic acid) has the same configuration as dextrorotatory glyceric acid (see p. 311) and the natural protein amino-acids.

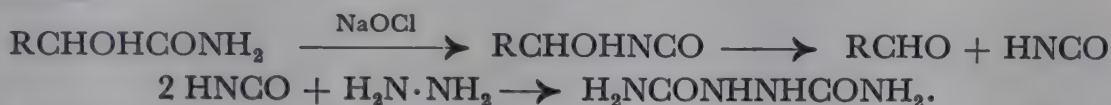
Since lactic acid is readily obtainable by fermentation processes, and has thus become a cheap substance, it has found some use in industry. In tanning it is used for removing lime from hides, and in dyeing for the reduction of chromates in chromate mordanting. It is also added to lemonades, essences, etc. It is used in medicine as a corrosive.

Antimony lactate is used as a mordant in printing and dyeing. Titanium lactates are used in tanning. Calcium lactate finds application in medicine as a non-irritant calcium preparation (magnesium lactate is a purgative). The syrupy potassium and sodium lactates were used as substitutes for glycerol, etc.

Lactic acid, like glycolic acid, tends to form anhydrides. Several of these are known, e.g. lactic anhydride, $\text{CH}_3\text{CH}(\text{OH})\text{CO}\cdot\text{OCH}(\text{CH}_3)\text{COOH}$, and the cyclic lactide, which is obtained by prolonged heating of the acid:



The amides of the α-hydroxycarboxylic acids are degraded like other amides on treatment with halogen and alkali. The intermediate isocyanate compounds formed break down, however, into aldehydes and isocyanic acid. The latter can be detected by means of hydrazine, as the amide of hydrazodicarboxylic acid (Weerman's reaction for the detection of α-hydroxy-acids):



β-HYDROXYPROPIONIC ACID, ETHYLENE LACTIC ACID, $\text{CH}_2\text{OHCH}_2\text{COOH}$, is formed from β-iodopropionic acid by heating with water, or from acrylic acid by the addition of the elements of water by means of sodium hydroxide:



It is a syrupy liquid. Dehydrating agents convert it into acrylic acid, not into an anhydride.

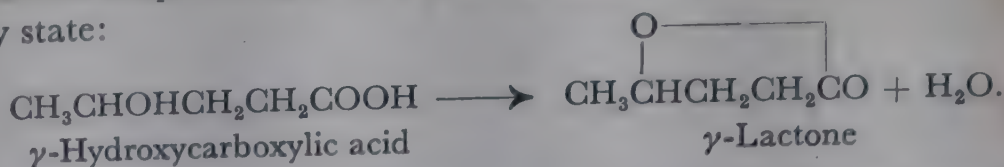
β-HYDROXYBUTYRIC ACID, $\text{CH}_3\text{CHOHCH}_2\text{COOH}$. The lævorotatory form of β-hydroxybutyric acid is sometimes contained in urine, and is especially abundant in cases of diabetes mellitus, usually together with acetone and acetoacetic acid, $\text{CH}_3\text{COCH}_2\text{COOH}$. It is probably formed from the latter by reduction, but can on the other hand be oxidized again in the organism to acetoacetic acid, the latter being then further decomposed to acetone and carbon dioxide.

The melting point of the active forms is 46–48°. Their specific rotation is 25.0°.

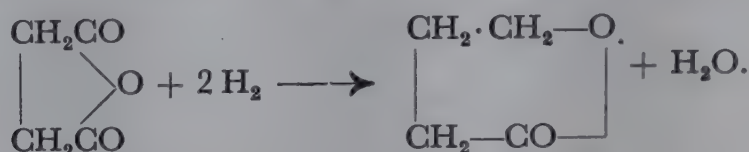
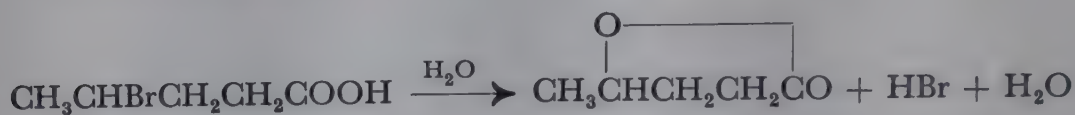
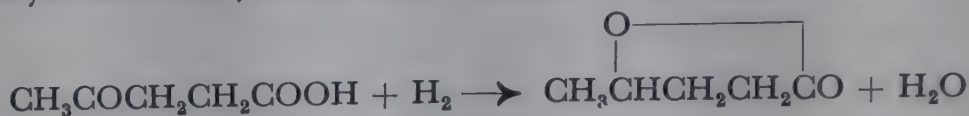
γ-HYDROXY-ACIDS. The acids which contain the OH group in the γ-position are very unstable, and are hardly ever obtained in the free state, since they readily anhydridize to γ-lactones, compounds which were extensively investigated by Fittig. The *lactones* are internal esters of hydroxycarboxylic acids. The most stable are the γ-lactones which contain a five-membered ring; δ-lactones can also be prepared, though with greater difficulty, and the ring opens more easily. The formation of ε-lactones and β-lactones is not general. Only a few representatives of this group are known. They are prepared by special methods (e.g. β-propiolactone can be made from formaldehyde and ketene:



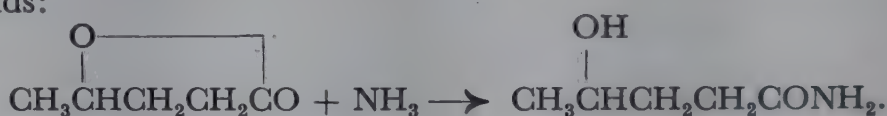
The formation of the γ -lactones from the γ -hydroxycarboxylic acids usually occurs even on evaporating their aqueous solutions, and at any rate on heating in the dry state:



Also, syntheses which should lead to the formation of γ -hydroxycarboxylic acids often give the γ -lactones instead, e.g. the reduction of γ -keto-carboxylic acids, heating γ -halogen-substituted fatty acids with water, or the reduction of dicarboxylic acid anhydrides with sodium amalgam in acid solution:



The breaking of the lactone ring occurs with differing ease for the different γ -lactones. The reversion into the hydroxy-acids by heating with water reaches an equilibrium state. Ammonia also opens the ring, and produces amides of the γ -hydroxy-acids:

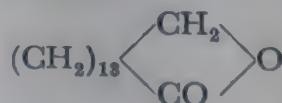


The reduction of γ -lactones is important from the preparative point of view. In the case of the polyhydroxy- γ -lactones (lactones of the sugar acids) this gives hydroxy-aldehydes (aldoses) directly.

δ -HYDROXYCARBOXYLIC ACIDS. They are obtained, for example, by the reduction of δ -keto-carboxylic acids, and can be converted into δ -lactones. The latter, however, as mentioned above, are not so stable as the γ -lactones, and the ring opens more easily:

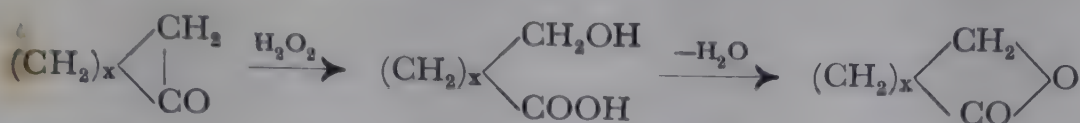


On the other hand, according to the investigations of Kerschbaum, lactones with multimembered rings again possess greater stability. These highly interesting substances are even constituents of the essential oils of plants. The musk-smelling principle of the oil from angelica root has been identified as the lactone of 15-hydroxypentadecanoic acid:



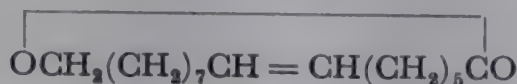
It can be prepared artificially from 15-bromopentadecanoic acid and silver oxide, but better by the oxidation of *cyclopentadecanone* (see Ch. 58) with Caro's acid, or by depolymerization of linear poly-esters of 15-hydroxypentadecanoic acid (Carothers). It melts at 31–32°, and boils at 176° (15 mm).

Other higher cyclic ketones can be oxidized to 14–18 membered lactone rings in the same way as *cyclopentadecanone*. ω -Hydroxy-acids are probably intermediate products in the reaction:



Good yields of multimembered lactones are afforded by the action of potassium carbonate on ω -halogeno-fatty acids in extremely dilute solutions (H. Hunsdiecker).

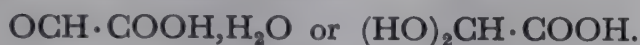
The similarly constituted lactone of 16-hydroxy-7-hexadecenoic acid occurs in musk-seed oil. It is known as *ambrettolide*, and likewise smells of musk:



For the stability of multimembered ring systems, see Ch. 58.

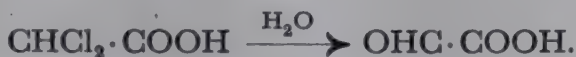
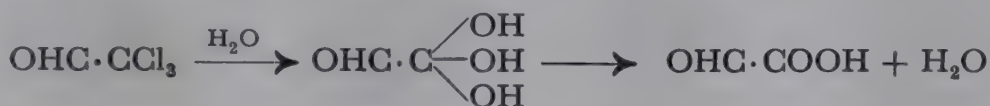
Aldehydic carboxylic acids

GLYOXYLIC ACID (or glyoxalic acid),



This acid is present in unripe fruit, but disappears gradually during ripening.

It can be prepared by the oxidation of glycol, glycolic acid, or alcohol with nitric acid, or it can be obtained by heating chloral or dichloroacetic acid with water. These syntheses prove its structure:



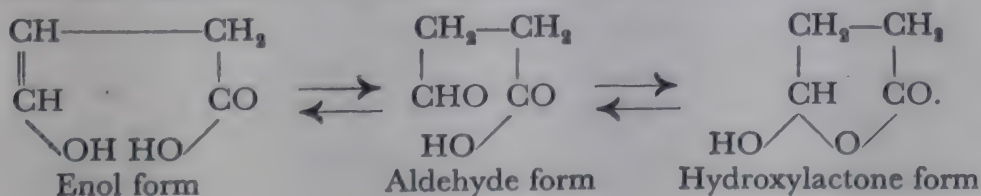
Recently glyoxylic acid has been produced also technically by the electrolytic reduction of oxalic acid using mercury or lead electrodes.

The compound shows the reactions of a carboxylic acid and an aldehyde. The reduction of ammoniacal silver nitrate and the formation of a hydrazone are due to the aldehydic group. On heating with alkali, glyoxylic acid disproportionates into glycolic acid and oxalic acid:

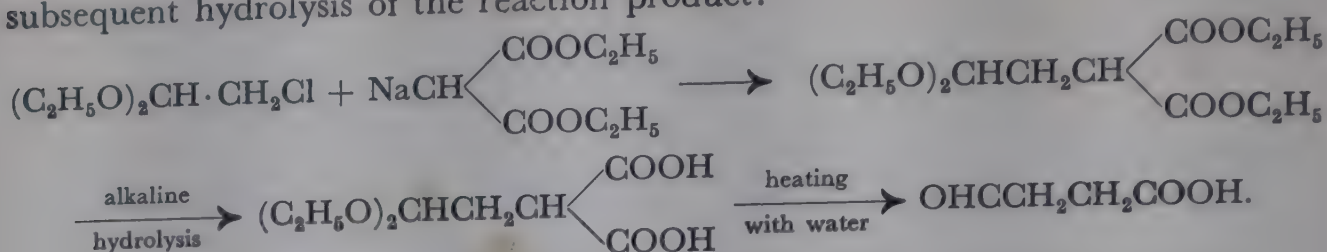


Since it retains firmly one molecule of combined water, it may be regarded as the acid of an aldehyde hydrate, $(\text{HO})_2\text{CH}\cdot\text{COOH}$. Anhydrous glyoxylic acid can be obtained by the evaporation of aqueous solutions over sulphuric acid or phosphorus pentoxide *in vacuo*. It is a colourless, hygroscopic syrup.

Further representatives of HOMOLOGOUS ALDEHYDIC ACIDS are known. Some of them may exist in a tautomeric (hydroxylactone) form in addition to the true aldehydic form. Moreover, they can react, under certain circumstances, in the enol form:



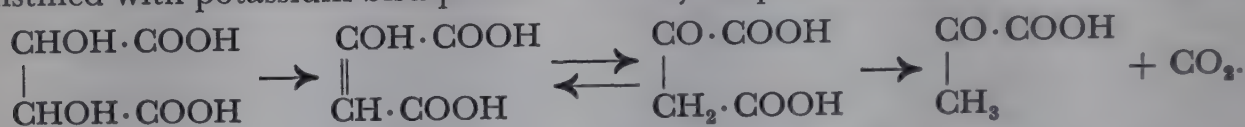
A method of preparation by which some compounds of this group are obtainable, depends on the condensation of chloracetals with malonic ester, and subsequent hydrolysis of the reaction product:



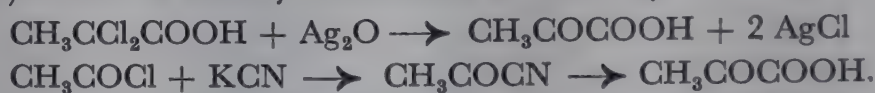
Keto-carboxylic acids

According to the relative positions of the carbonyl and carboxyl groups, α -, β -, and γ -ketonic acids etc. are recognized. Each of these classes of compounds possesses its own special characteristics.

Pyruvic acid, $\text{CH}_3\text{COCO}_2\text{H}$. This compound is not only the simplest, but is also the most important of the α -keto-carboxylic acids. It can be obtained from tartaric acid or racemic acid by distillation, and in particularly good yield when distilled with potassium bisulphate. Probably the process takes the following course:



The acid was discovered in this way by Berzelius, and up to the present no better method of preparation has been found. However, there are many other methods of formation, e.g. the hydrolysis of α,α -dichloropropionic acid with water and silver oxide or the hydrolysis of acetyl cyanide (the nitrile of pyruvic acid) which is readily obtainable from acetyl chloride:

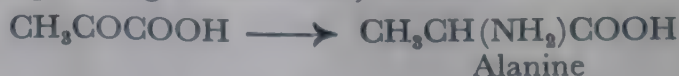


Pyruvic acid is a liquid boiling at 165° , and melting at 13.6° . It has a pungent odour, is miscible with water, and possesses a dissociation constant of 5.6×10^{-3} , which is high for a carboxylic acid. The keto-group easily reacts with hydroxylamine (giving an oxime), and phenylhydrazine (giving a phenylhydrazone). It reduces ammoniacal silver nitrate, and is easily converted by adding on hydrogen (sodium amalgam) into lactic acid. Oxidation converts it into acetic acid and carbon dioxide:



The behaviour of pyruvic acid towards concentrated sulphuric acid is very characteristic. Even on gentle heating with it carbon monoxide is evolved. All known α -ketonic acids give this reaction, and it can, therefore, be used for their detection. However, there are α -hydroxycarboxylic acids (such as tartaric acid) which behave similarly, i.e. give carbon monoxide on treatment with sulphuric acid.

Pyruvic acid is an intermediate product in the decomposition of sugars in alcoholic fermentation (see p. 89) and is then further decomposed to acetaldehyde with elimination of carbon dioxide. In the organism it can be converted (in the liver) into the corresponding amino-acid, *alanine*:



Other α -keto-acids behave in a similar way.

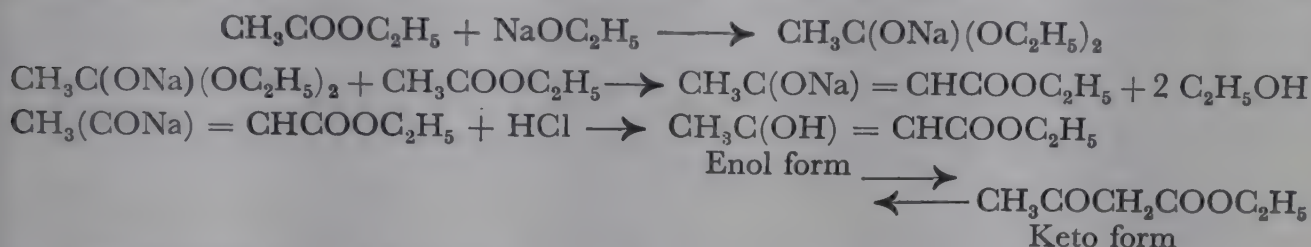
Pyruvic acid is used industrially for the manufacture of *atophan* (see Ch. 61) and its derivatives, which are employed for relieving gout.

Acetoacetic acid, $\text{CH}_3\text{COCH}_2\text{COOH}$. The *free* β -ketonic acids are very unstable substances, decomposing very readily into carbon dioxide and ketones. They are, therefore, seldom used. Their salts, and particularly their esters, are much more stable, and the latter, on account of their great reactivity, are among the most important substances in preparative chemistry. The simplest of them, and at the same time the most interesting, is ethyl acetoacetate (or simply *acetoacetic ester*), $\text{CH}_3\text{COCH}_2\text{COOC}_2\text{H}_5$.

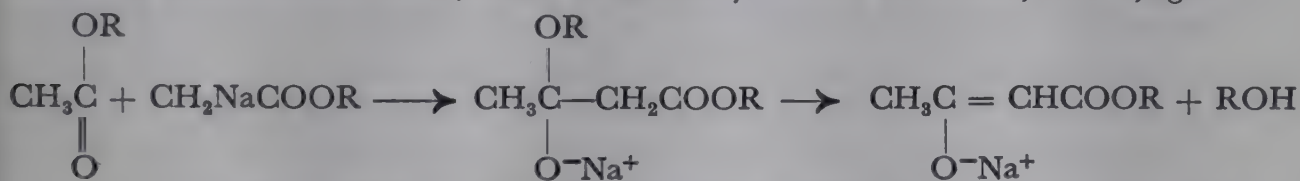
Its preparation is based on the condensation of two molecules of ethyl acetate under the influence of sodium, sodium ethylate, or sodamide (Geuther, W. Wislicenus, Claisen):



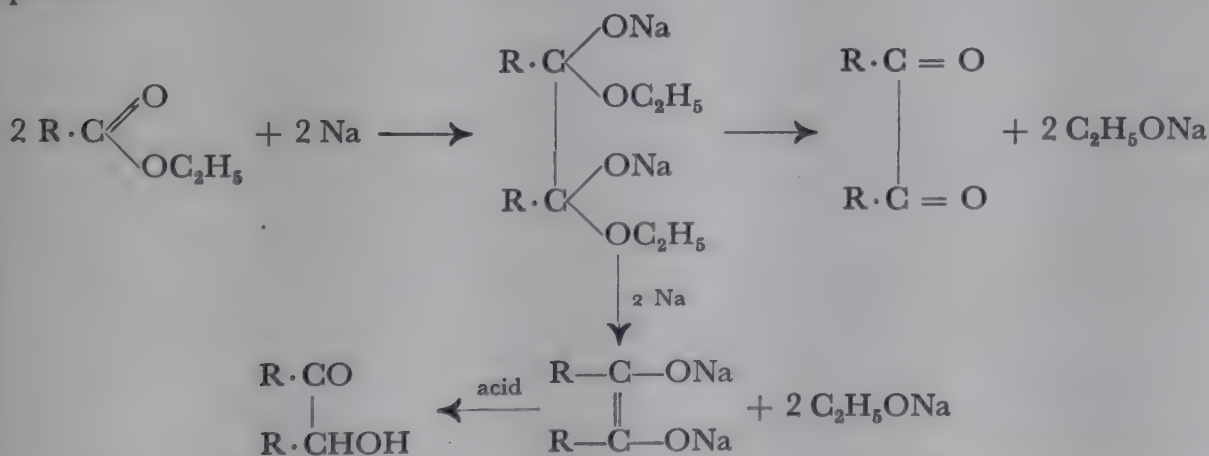
Many experiments have been carried out and different views have been expressed concerning the mechanism of this important reaction. Claisen put forward the view that the sodium ethylate (which could also be gradually formed by the use of sodium alone from the metal and the alcohol formed in the synthesis) first adds on to a molecule of the ethyl acetate and this addition product then combines with a second molecule of ethyl acetate to form sodio-acetoacetic ester:



Other views are put forward, at present, concerning the mechanism of the acetoacetic ester formation. Thus, according to Arndt, the first, reversible phase of the reaction consists in the addition of one molecule of the monosodium derivative of ethyl acetate ("methylene component") to the carbonyl group of a second molecule of ethyl acetate ("ester component"). In the second, irreversible phase a proton and an [OR]-anion are liberated under the action of more alkali, which immediately form an alcoholate, RONa , again:



If metallic sodium is used in place of sodium ethylate in the acetic ester condensation, diketones and acyloins (i.e. compounds of the type $\text{R}\cdot\text{CHOHCO}\cdot\text{R}$) are often produced as by-products. These are believed to be formed according to the following equations:



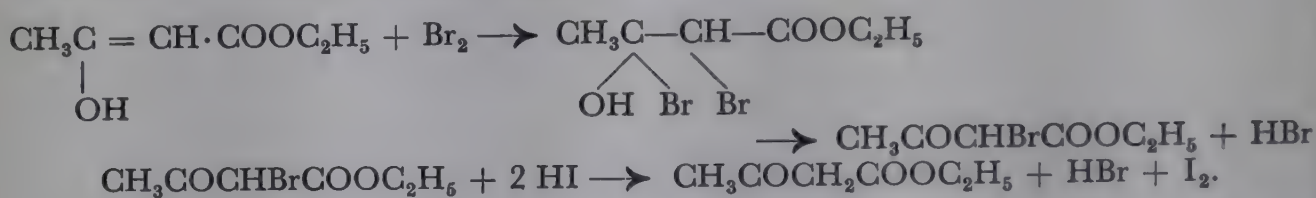
ACETOACETIC ESTER is the classical example of a *tautomeric substance*. Its

constitution has been made the object of numerous investigations, which, not only in elucidating this individual case, have been of great importance for explaining questions of tautomerism:



The enol form contains a carbon double bond, and therefore must tend to add on substances, e.g. halogens. On the other hand, it can be predicted that it will possess acid properties, since these occur in all compounds which have a hydroxyl group attached to a carbon atom linked to another by a double bond. In fact, various salts of acetoacetic ester have been prepared, the sodium and potassium salts being especially important in syntheses, whilst the iron salt, on account of its intense red colour deserves mention.

K. H. Meyer based a method of determining the enol form in the presence of the keto form on the unsaturation of the former. The method depends on the fact that only the enol form adds on bromine instantaneously. Very labile α -bromoketones are thus formed which liberate iodine from hydrogen iodide. The determination of the liberated iodine gives a measure of the amount of the enol form of acetoacetic ester present:



It was shown by this method that ordinary ethyl acetoacetate contains about 7.4–8 per cent. of enol, and about 92 per cent of the keto form. It thus contains two tautomeric forms (allelotropic mixture). When, however, the compound is obtained from its sodium salt by acidification, its enol-content immediately after its isolation amounts to as much as 80 per cent. This gradually falls on long standing and finally remains at about 8 per cent which is the amount present in the commercial ester. This provides a confirmation of the view expressed above that sodio-acetoacetic ester is derived from the enol form. These experiments also prove that the enol and keto forms can be converted spontaneously one into the other.

A further confirmation of the presence of the isomerides in the liquid substance is provided by the isolation of the two desmotropic forms by Knorr.

On cooling ordinary acetoacetic ester to -78° , a well-crystallized form separates, which differs only slightly in its constants from "equilibrium" acetoacetic ester, though the red colour with ferric chloride takes some time to appear at low temperatures. Obviously this is the keto form. On the other hand, by separating the ester from its sodium salt at -78° , Knorr was able to prepare a liquid which possessed a considerably higher refractive index, and gave an intense red colour with ferric chloride immediately on addition, thus showing that it contained a high percentage of the enol form. This liquid did not solidify at -78° .

By this separation of the two desmotropic forms, the problem of the tautomerism of acetoacetic ester was largely solved. Later, K. H. Meyer found a still simpler method of separating the two isomerides. If all substances tending to

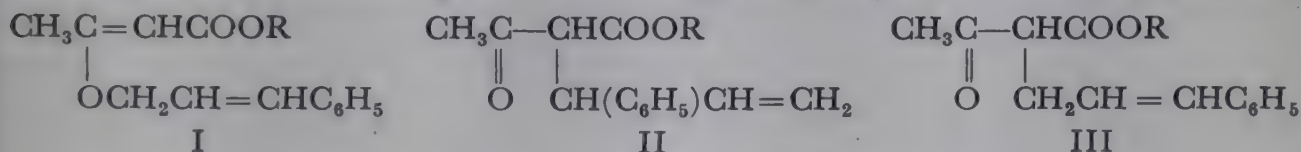
enolize the ester, particularly alkali from the glass, are excluded, it is possible to fractionate acetoacetic ester from quartz flasks. The enol form collects mainly in the first fractions of the distillate, and the residue is the pure ketonic form. The enol-content of four fractions of equal volume was:

1st fraction	22.0 %	enol.
2nd fraction	11.0 %	enol.
3rd fraction	2.5 %	enol.
Residue	0.0 %	enol.

The hydrolysis of the enol acetate of acetoacetic ester with 1 per cent oxalic acid also yields the pure enol form.

The reactions of acetoacetic ester with acid chlorides and alkyl halides are especially important from the preparative point of view. The free esters is not often used as a starting point (though it does react with acid chlorides in pyridine), but generally the salts, particularly sodio-acetoacetic ester. This is derived, as mentioned above, from the enol form, and it is, therefore, rather surprising that it always gives C-alkyl derivatives with alkyl halides. With acid chlorides, on the other hand, it reacts in two ways. In addition to the C-acyl derivatives, compounds are formed in which the acid radical is attached to the oxygen atom. Whilst the formation of O-derivatives from the sodium enolate of acetoacetic ester and the organic halogen component by double decomposition can be readily understood, it is more difficult to explain the formation of C-alkyl and C-acyl derivatives of acetoacetic ester. The older view of Claisen, that in these cases too, the oxygen derivative is the initial product of the reaction, which subsequently rearranges to the corresponding C-derivative, seems to be no longer tenable. From various observations it must be concluded instead, that in the alkylation and acylation of acetoacetic ester, direct substitution at the C-atom largely occurs.

Thus, for example, compound I rearranges to II, whilst the direct action of cinnamyl bromide, $\text{C}_6\text{H}_5\text{CH}=\text{CHCH}_2\text{Br}$, on sodio-acetoacetic ester gives III. Compound I cannot, therefore, be an intermediate product in the latter reaction (W. M. Lauer, E. I. Kilburn):



Similar syntheses give rise to homologues of acetoacetic ester of the type $\text{CH}_3\text{COCHR}\text{COOC}_2\text{H}_5$, and esters of diketo-carboxylic acids of the formula $\text{CH}_3\text{COCHCOOC}_2\text{H}_5$. It is possible to break down acetoacetic ester and its



homologues and derivatives into simple carboxylic acids or simple ketones, according to the experimental conditions, and this is particularly important.

Heated with *concentrated* alkali, acetoacetic ester breaks down chiefly according to the equation:



Its homologues break down under these conditions as follows:



This is called the *acid hydrolysis* of acetoacetic ester. It gives rise to fatty acids, and is an important method of preparing them.

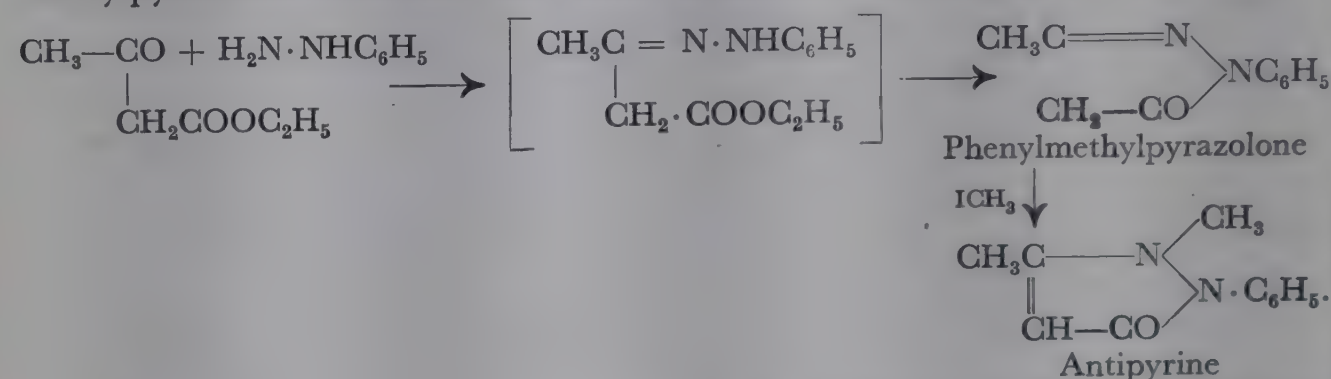
Dilute alkali hydrolyses acetoacetic ester and its homologues in such a way as chiefly to give ketones.

Ketonic hydrolysis. Since this reaction proceeds quite smoothly, and the homologues of acetoacetic ester can readily be synthesized, this is a useful method of synthesizing ketones:

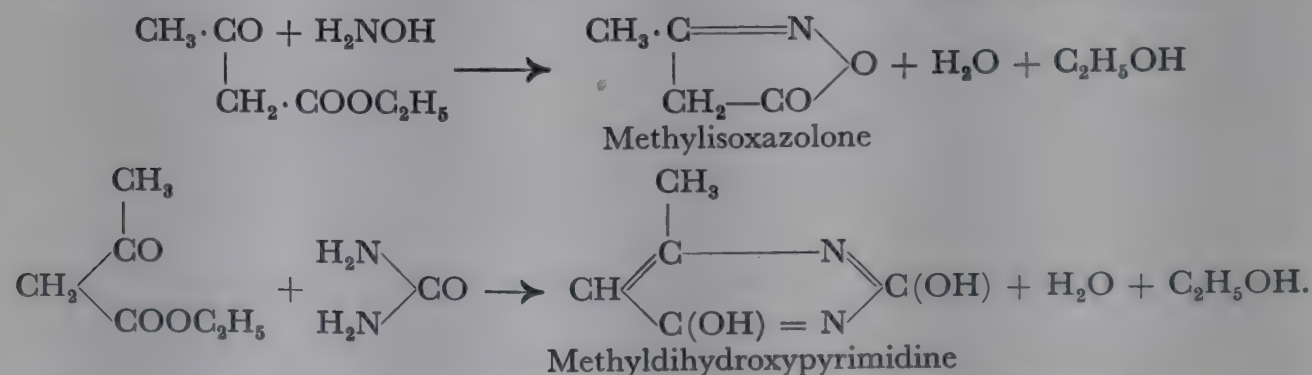


The ketonic hydrolysis is also an important reaction from the biological point of view. It was mentioned in another place that the oxidation of fatty acids (see p. 197) in the organism gives rise to ketones through the β -hydroxy- and β -keto-carboxylic acids, and that the rancidity of fats (see p. 217) is due to the conversion of fatty acids into β -keto-carboxylic acids and of these into ketones by the action of moulds.

The keto-group of acetoacetic ester reacts readily with reagents which characterize that group. These reactions, as in the case of the β -diketones, often lead to the formation of ring-compounds. For example, with phenylhydrazine phenylmethylpyrazolone is formed, from which *antipyrine* is obtained by methylation:



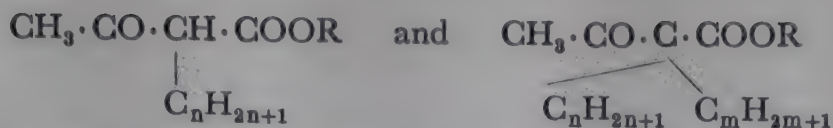
With hydroxylamine, acetoacetic ester gives *methylisoxazolone*, and with urea it gives a derivative of the six-membered heterocyclic compound, *pyrimidine*:



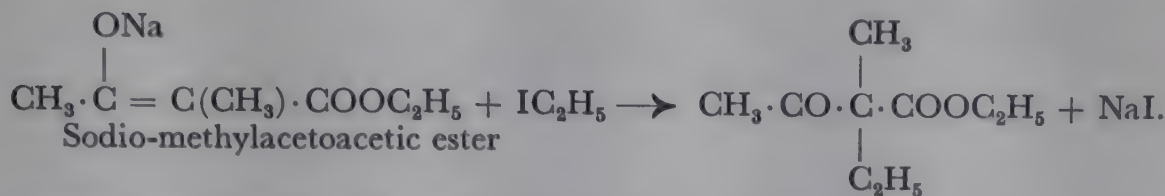
Acetoacetic ester is a colourless, pleasant smelling liquid, which boils at 181° . Free acetoacetic acid can be obtained from its sodium salt by careful acidification and extraction with ether, as a crystalline mass, which is very unstable, and decomposes readily with elimination of carbon dioxide into acetone. Its occurrence in the urine of diabetic patients, amongst the "acetone bodies", has already often been referred to. It can be reduced in the organism to β -hydroxybutyric acid (see p. 263) and be formed again by oxidation of the latter.

Acetoacetic ester is used amongst other things for the technical preparation of numerous pyrazolone dyes, and drugs, such as antipyrine, pyramidone, etc., and for the synthesis of substances serving research purposes.

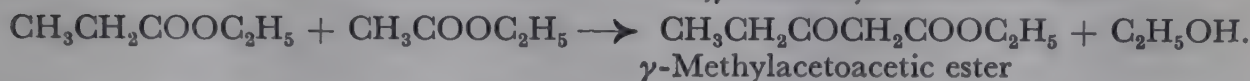
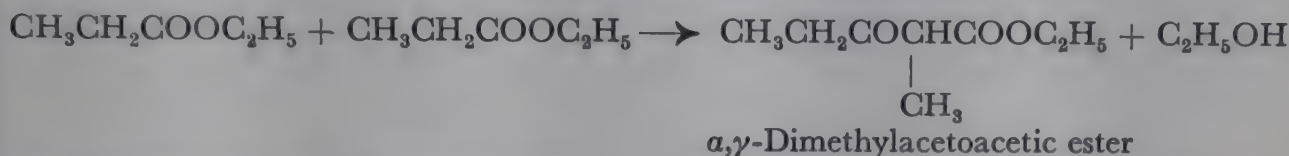
Homologous ketonic carboxylic acids, HOMOLOGUES OF ACETOACETIC ESTER, are known in great numbers. For those of the type:



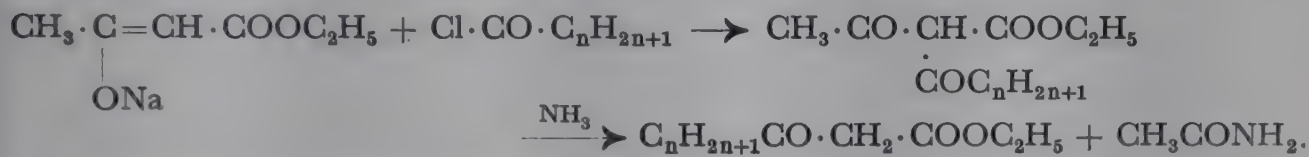
a single or double alkylation of acetoacetic ester is the most convenient method of preparation. The second alkyl group to be introduced may be different from the first:



Homologues of another kind can be obtained by the condensation of esters of the higher fatty acids:

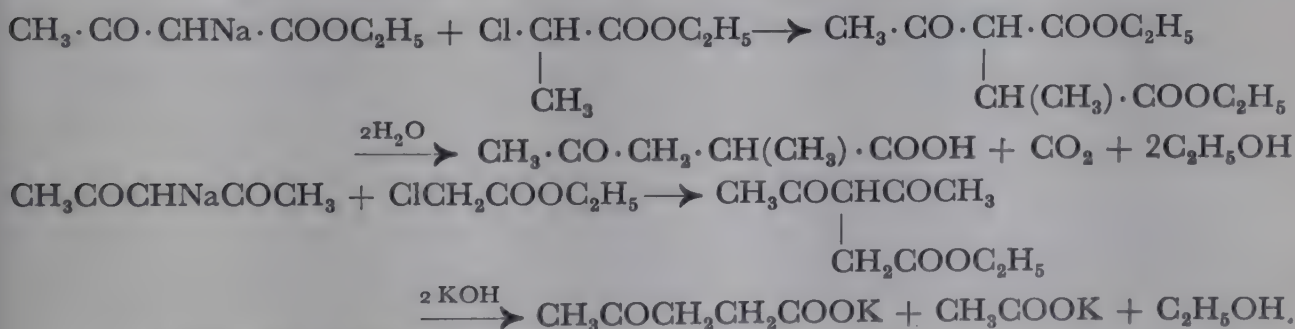


Starting with the C-acyl derivatives of acetoacetic ester it is possible to obtain homologues of acetoacetic ester by removing the $\text{CH}_3\text{CO}-$ group by means of ammonia or sodium ethylate:

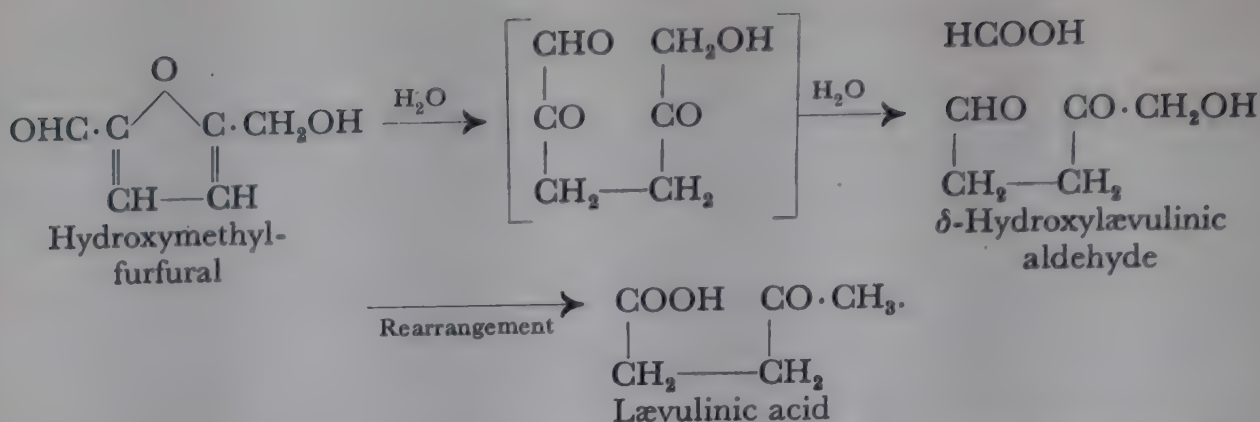


The chemical properties of the homologues of acetoacetic ester are completely analogous to those of the parent substance. Some of them occur as intermediate compounds in natural processes (cf. the rancidity of fats).

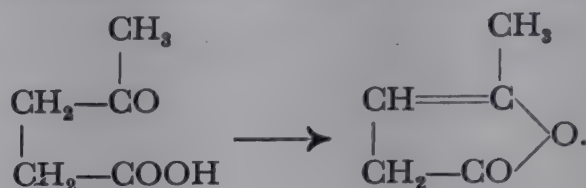
Lævulinic acid, $\text{CH}_3\text{COCH}_2\text{CH}_2\text{COOH}$. The γ -keto-acids can be prepared by acting on α -halogen-substituted fatty acids with acetoacetic ester or acetylacetone, and submitting the product to alkaline hydrolysis:



The simplest γ -keto-carboxylic acid, *lævulinic acid*, is usually, however, obtained by another method. It is formed in good yield by heating sugars (Tollens), the hexoses, such as fructose, glucose, and galactose, with concentrated hydrochloric acid. The reaction is so characteristic for sugars with six carbon atoms that it can be used for their detection. The reactions which lead from the carbohydrate to lævulinic acid are of a complicated nature. The first reaction product is hydroxymethyl-furfural (see Ch. 59), which, as Kiermayer showed, can be quantitatively converted into lævulinic acid and formic acid. Perhaps δ -hydroxy-lævulinic aldehyde is formed as an intermediate product (Pummerer):



Lævulinic acid is a crystalline solid melting at 37° . It can be distilled without decomposition (boiling point about 250°), and thus does not break down giving carbon dioxide as the β -keto-carboxylic acids do. By continued heating, however, it loses water intramolecularly and forms an internal anhydride:



CHAPTER 17. CYANOGEN. DICARBOXYLIC ACIDS

I. Cyanogen, NC-CN

Free *cyanogen*, or “dicyanogen” has been detected spectrographically in comets, and is found in small amounts in blast-furnace gases. To prepare it, the same reaction is generally used even to-day as that by which it was discovered by Gay-Lussac, namely the action of heat on mercuric cyanide:



Cyanogen can also be obtained by the action of potassium cyanide solution on copper sulphate:



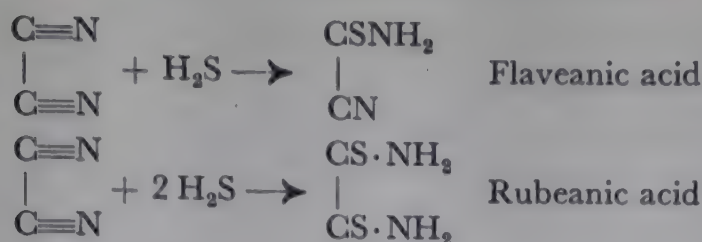
or from ammonium oxalate by removing water by means of phosphorus pentoxide:



This last method of preparation proves the constitution of cyanogen. It is the nitrile of oxalic acid, and cyanogen can be converted into this acid by acid hydrolysis.

Cyanogen has a pungent smell. It boils at -20.7° , and melts at -34.4° . It is a poisonous, strongly endothermic compound, which burns with a very hot violet flame, with a red border. It dissolves to a considerable extent in water, but the solution rapidly decomposes depositing brown flocks (azulmic acid). On long heating at 400° it is converted into a polymeric modification, *paracyanogen*. The latter is a brown, amorphous powder, and is also obtained as a by-product in the preparation of cyanogen.

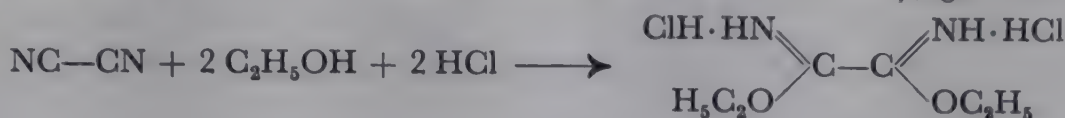
Hydrogen sulphide adds on to cyanogen in a similar way as water. Thio-amides of oxalic acid, the yellow *flaveanic acid*, and the red *rubeanic acid* are formed:



Cyanogen reacts with alkalis in a manner very similar to the halogens, forming alkali cyanide and alkali cyanate:

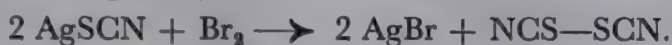


Of other addition reactions with the nitrile group may be mentioned that with alcohol and hydrochloric acid, which, in the normal way, gives an imido-ether:



II. Free thiocyanogen, NCS-SCN

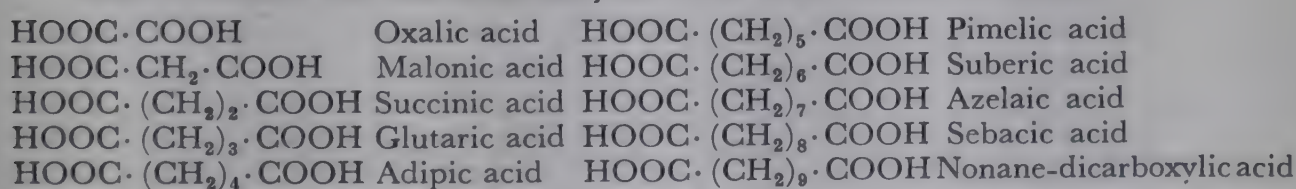
Free thiocyanogen has only recently been prepared by Söderback by acting on silver, lead, or mercuric thiocyanate with bromine or iodine in indifferent solvents (e.g. carbon disulphide):



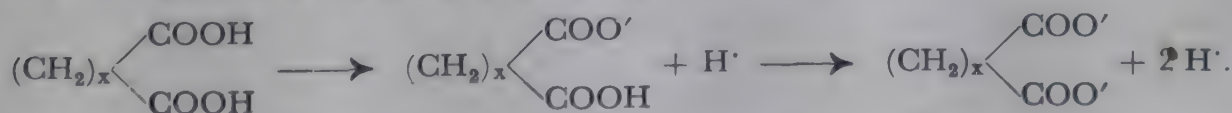
Later it was found that thiocyanogen could also be obtained by electrolysis of the alkali thiocyanates. It is a very unstable compound which can be crystallized from carbon disulphide. It melts at -3° . It shows even greater analogies with the halogens than those shown by cyanogen. Metals, even gold, are converted into thiocyanates by solutions of thiocyanogen; thiocyanogen can substitute other elements or groups in many organic substances, the group-SCN replacing one hydrogen atom. Thiocyanogen is decomposed by water. Probably in addition to thiocyanic acid the unstable hypothiocyanic acid $\text{HO}\cdot\text{SCN}$ is formed, which, however, decomposes so that hydrocyanic acid and sulphuric acid are found among the decomposition products.

III. Saturated dicarboxylic acids

The first nine normal dicarboxylic acids bear common names:



They are solid substances which crystallize well. The first members are readily soluble in water, the higher members less soluble, those acids with odd numbers of carbon atoms being always more soluble than those with even numbers. The solutions react acid. The dissociation takes place in two steps, first to the monovalent, and second to the divalent negative ion:



Compared with the fatty acids (see p. 194), the dicarboxylic acids possess

higher dissociation constants, and are therefore stronger acids. This is especially the case for oxalic acid (see the table below).

Not only in connection with solubility, but also with regard to melting point there is an oscillation within the homologous series. The acids with even numbers of carbon atoms melt at a higher temperature than those with an odd number. In contrast to the corresponding relationships for the fatty acids, the melting points of the dicarboxylic acids *fall* with increasing molecular weight, at least, within the series with even numbers of C-atoms:

		M.p.	Solubility	Dissociation	
			in %, in water at 20°	constants	
				k_1	k_2
Oxalic acid	HOOC ² COOH	189.5	8.6	$3.8 \cdot 10^{-2}$	
Malonic acid	HOOC(CH ₂)COOH	133	73.5	$177.0 \cdot 10^{-5}$	$4.37 \cdot 10^{-6}$
Succinic acid	HOOC(CH ₂) ₂ COOH	183	5.8	$7.36 \cdot 10^{-5}$	$4.50 \cdot 10^{-6}$
Glutaric acid	HOOC(CH ₂) ₃ COOH	97.5	63.9	$4.60 \cdot 10^{-5}$	$5.34 \cdot 10^{-6}$
Adipic acid	HOOC(CH ₂) ₄ COOH	153	1.5	$3.90 \cdot 10^{-5}$	$5.29 \cdot 10^{-6}$
Pimelic acid	HOOC(CH ₂) ₅ COOH	105.5	5.0	$3.33 \cdot 10^{-5}$	$4.87 \cdot 10^{-6}$
Suberic acid	HOOC(CH ₂) ₆ COOH	140	0.16	$3.07 \cdot 10^{-5}$	$4.71 \cdot 10^{-6}$
Azelaic acid	HOOC(CH ₂) ₇ COOH	108	0.24	$2.82 \cdot 10^{-5}$	$4.64 \cdot 10^{-6}$
Sebacic acid	HOOC(CH ₂) ₈ COOH	134	0.10	$2.8 \cdot 10^{-5}$	
Nonane-dicarboxylic acid	HOOC(CH ₂) ₉ COOH	110			
Decane-dicarboxylic acid	HOOC(CH ₂) ₁₀ COOH	126			
Undecane-dicarboxylic acid	HOOC(CH ₂) ₁₁ COOH	112			

The chemical properties of the dicarboxylic acids are naturally governed principally by the carboxyl groups. All reactions of the fatty acids in which the carboxyl group takes part are found again in the dicarboxylic acids, only as a rule the effect is doubled.

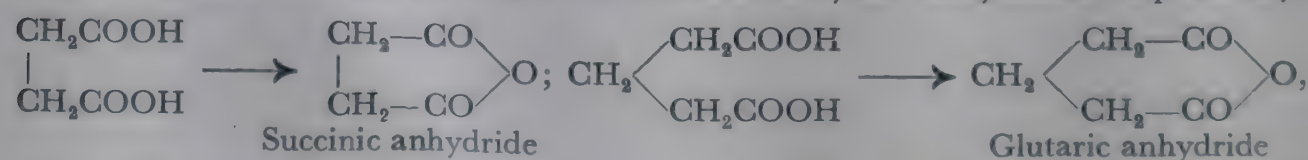
However, new reactions also make their appearance, having their origin in the mutual influence of the two carboxyl groups, or governed by their special positions. Special interest is attached to the behaviour of the dicarboxylic acids on heating. Oxalic acid readily decomposes into formic acid and carbon dioxide when heated:



Malonic acid is also unstable towards heat. Whenever two carboxyl groups are attached to the same carbon atom one of them is readily removed on heating. Malonic acid and its derivatives decompose in this way into carbon dioxide and fatty acids:



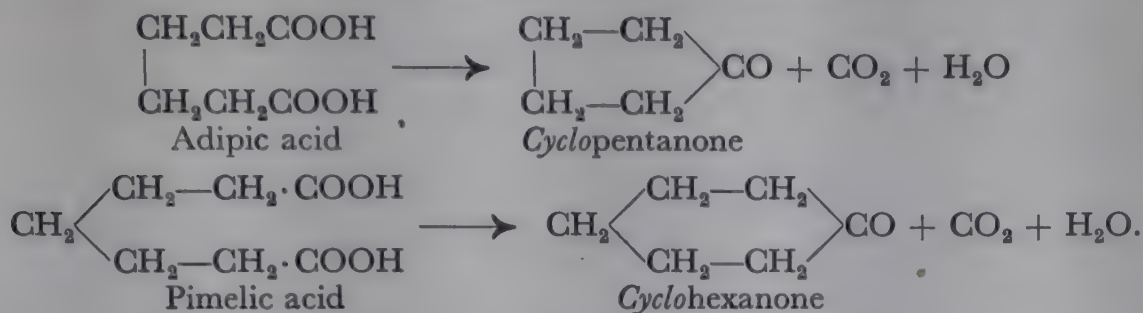
The behaviour of the next two members, succinic and glutaric acids, is quite different. By heating or treatment with acetyl chloride or acetic anhydride, they lose water and form the five- and six-membered cyclic anhydrides respectively:



Adipic acid produces on heating a *polymeric* anhydride, which is partly transformed into the very unstable monomolecular anhydride by distillation *in vacuo*.

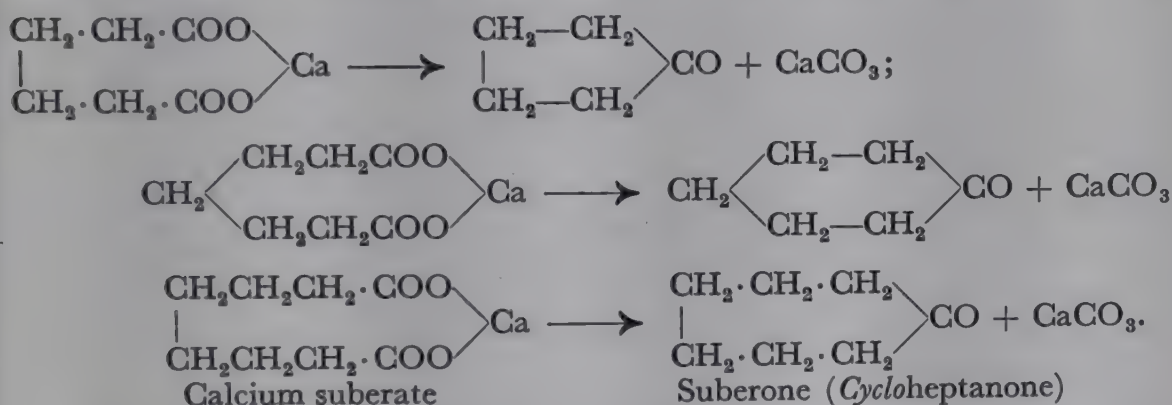
The higher dicarboxylic acids do not give such internal anhydrides. This provides another example of the stability and the favoured arrangement of the

five- and six-membered rings. These facts receive additional weight from the work of Blanc, who observed that adipic acid and pimelic acid give, on distillation with acetic anhydride, cyclic derivatives, though not the anhydrides, but ketones with again five- and six-membered rings respectively:



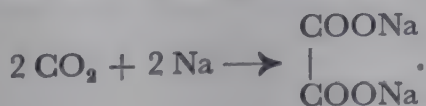
This varying behaviour of the dicarboxylic acids may be put to practical use in the determination, in a dicarboxylic acid of unknown constitution, of the position of the carboxyl groups with respect to each other (Blanc, Windaus).

Adipic acid and pimelic acid are also converted into *cyclopentanone* and *cyclohexanone*, respectively, by the dry distillation of their calcium salts. The analogous ring-closure also takes place with the calcium salts of suberic acid and azelaic acid, to give *cycloheptanone* and *cyclooctanone*, respectively, but with much poorer yield. On the other hand, cyclic ketones with nine members appear to be formed not at all or only in traces by this method (but see also Ch. 58):



Oxalic acid. In the form of its salts, oxalic acid is very widely spread in plants. Its insoluble calcium salt occurs in cell-walls and in the interior of the cells. Algæ, fungi, lichens, and ferns are rich in it, but it is also found in the higher plants. The acid potassium salt (salt of sorrel) is found in plants of the *Oxalis* and *Rumex* families; the sodium salt in *Salicornia* and *Salsola*; and the magnesium salt in the leaves of *Gramineæ*. The urine of animals and man always contains small quantities of calcium oxalate (more in pathological cases — oxaluria). It is also present in some animal organs. Ferrous and calcium oxalates are sometimes found as minerals.

Of the numerous methods of making this acid some have already been mentioned, such as the oxidation of glycol (see p. 246), the hydrolysis of cyanogen (see p. 272), and the rapid distillation of sodium formate (see p. 199), all of which give rise to oxalic acid. Further, the synthesis by the action of dry carbon dioxide on alkali metals is noteworthy. The gas is passed at 360° over sodium or potassium:

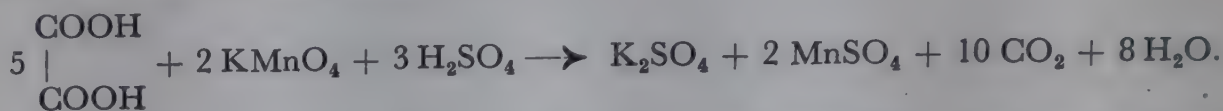


For the technical preparation of the acid its formation by fusing many organic substances, particularly carbohydrates, with alkalis is used. Sawdust is heated with the alkali to about 200° and the oxalic acid is extracted from the melt, after cooling, by water (Dale, 1856). It is purified by means of the insoluble calcium salt.

Oxalic acid crystallizes with two molecules of water, which it gives up at 100° . When treated with sulphuric acid it gives carbon dioxide, carbon monoxide, and water:

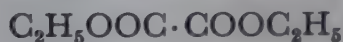


It is readily oxidized by potassium permanganate in acid solution to carbon dioxide and water. This reaction is made use of in volumetric analysis for standardizing potassium permanganate solution:

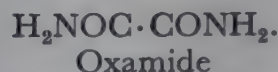


The chloride of oxalic acid, oxalyl chloride, $\text{ClOC} \cdot \text{COCl}$, is obtained by the action of phosphorus pentachloride on the anhydrous compound. It is a colourless liquid, boiling at 64° . It is used in syntheses.

An anhydride of oxalic acid is unknown, but neutral and acid esters:

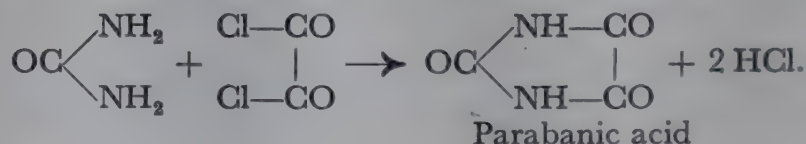


the oxamide and oxamic acid:

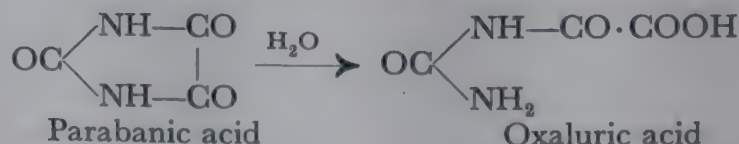


are known. The methods of preparing all these compounds are analogous to those used for the corresponding compounds of the fatty acids.

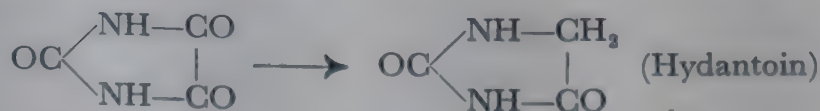
An important derivative of oxalic acid is the ureide, *parabanic acid* (oxalyl-urea), which is obtained synthetically from urea and oxalyl chloride:



Its formation by the oxidation of uric acid with nitric acid was of importance in deciding the constitution of uric acid. It is a crystalline compound, melting at $242\text{--}244^{\circ}$. When treated with alkalis it is broken down into *oxaluric acid*:

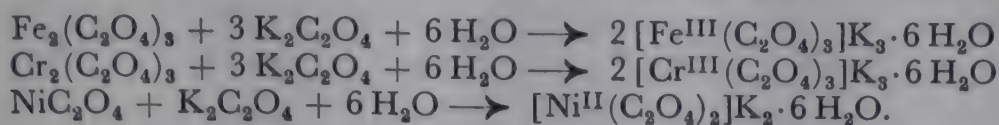


Its electrolytic reduction can be carried out in such a way as to give *hydantoin* (see p. 296).

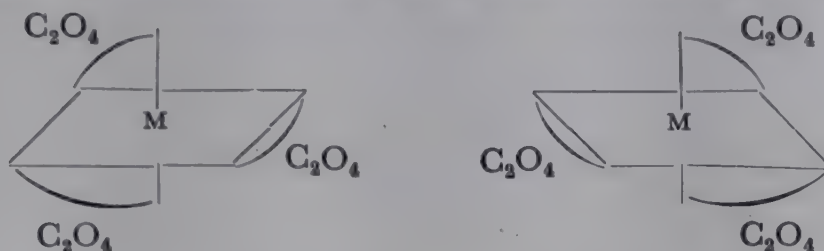


Various *metal salts of oxalic acid* have remarkable properties. As the acid is dibasic, two series of salts are known, the *neutral* and the *acid* salts. The neutral alkali oxalates are fairly easily soluble in water, the acid salts, on the other hand, being difficultly soluble. The alkaline-earth oxalates are almost insoluble. This property of calcium oxalate is made use of in analytical chemistry for the quan-

titative estimation of calcium and of oxalic acid. The heavy-metal oxalates are also insoluble in water, but many of them dissolve readily in solutions of the alkali oxalates. The reason for this is that the alkali-metal and the heavy-metal oxalates combine to form complexes, the "*oxalo-salts*", e.g.:



The structure of these complex salts is similar to that of other coordination compounds. Each oxalate radical takes up two coordination places. The space arrangement about the central atom is octahedral. Based on these constitutional formulæ it may be predicted that mirror-image isomerism is possible for the trioxalo-metal salts, and this was shown to be the case by A. Werner, who resolved trioxalochromates, trioxalocobaltates, and trioxalorhodiates into optically active forms:



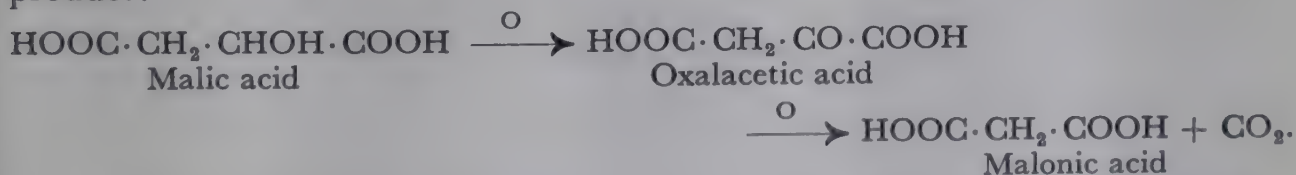
The solvent action of salt of sorrel for rust, etc., depends upon the solubility of the heavy-metal oxalates in solutions of the alkali oxalates.

Oxalic acid is used in industry as a mordant in cloth-printing, for the manufacture of dyes, dextrans, ink, as a bleaching agent (straw), as a precipitant for the rare earths, etc. By its electrolytic reduction, glycolic and glyoxylic acids are obtained. The aluminium and antimony salts are also used in dyeing.

Malonic acid, $\text{HOOCCH}_2\text{COOH}$. Malonic acid has been detected in beet juice. It is prepared from chloroacetic acid and potassium cyanide, which give cyanacetic acid, from which malonic acid is obtained by hydrolysis:



The compound was discovered during work on the oxidation of malic acid (Dessaigues), in which oxalacetic acid is formed as an unstable intermediate product:



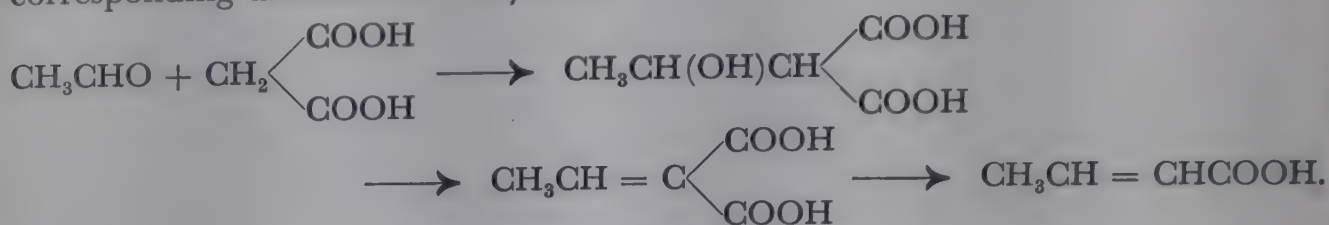
The melting point of the crystalline acid is 134° . Of its salts, only those of the alkali metals are readily soluble in water.

The behaviour of malonic acid and its C-alkyl derivatives on heating is very characteristic. They lose carbon dioxide, and give fatty acids. It is a quite general phenomenon that compounds containing two (or more) carboxyl groups attached to the same carbon atom are unstable at high temperatures:

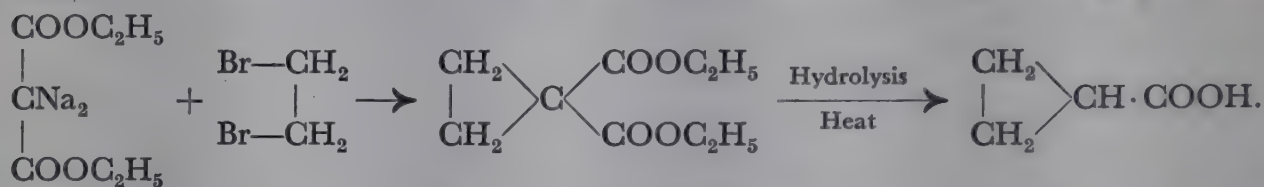


The activating effect of two negative substituents on a methylene group

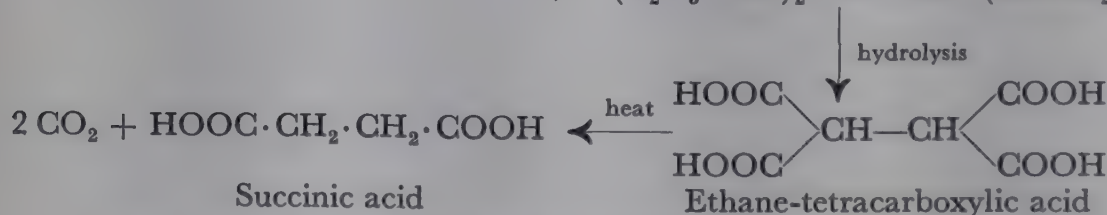
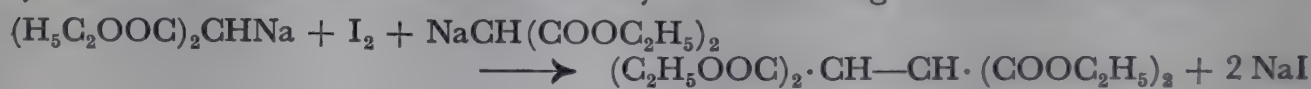
enclosed by them has already been mentioned in various other cases. Such an effect is also observed in malonic acid and its esters. Thus it is shown by the fact that the compound very easily condenses with aldehydes and ketones, whereby, under suitable experimental conditions, the aldol-like intermediate product (hydroxydicarboxylic acid) can be isolated. This, however, easily loses water giving an unsaturated dicarboxylic acid, which, on heating, is converted into the corresponding unsaturated fatty acid:



The labile nature of the methylene hydrogen atoms of malonic acid is shown particularly by the fact that in malonic ester they can be replaced by sodium, potassium, magnesium, etc. The mono- and disodio-malonic esters are exceedingly useful starting substances for syntheses, which, as regards mechanism and importance, correspond to the acetoacetic ester reactions. Sodio-malonic ester reacts with alkyl halides, and toluenesulphonic esters to give mono- and dialkyl-malonic esters. With chlorides of the carboxylic acids it gives ketodicarboxylic acids:



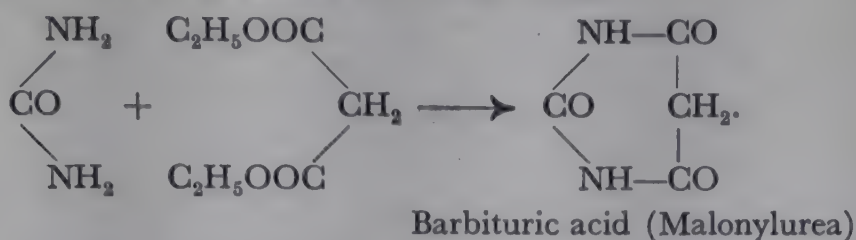
Succinic acid, the next higher homologous dicarboxylic acid, can also be synthesized from sodio-malonic ester by the following series of reactions:



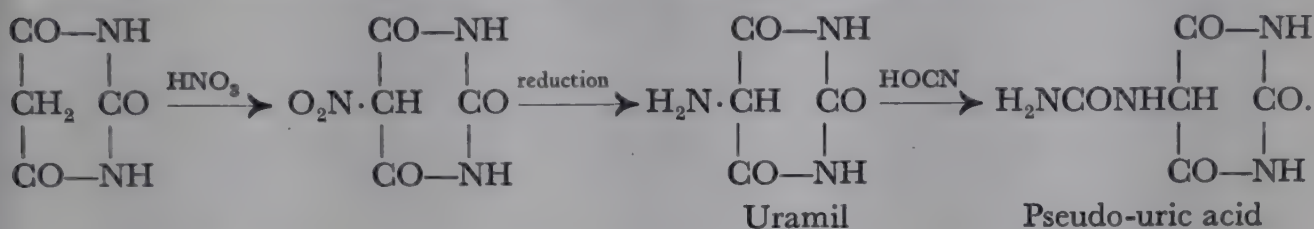
In the literature the question of whether the alkali-metal atom must be assumed to be linked to oxygen (as in the case of acetoacetic ester), or whether it is linked to the carbon atom, has been exhaustively discussed. It appears that the latter assumption is correct. If, for example, the sodium salt of the diethyl ester of malonic acid is treated with methyl iodide, and the sodium salt of the dimethyl ester of malonic acid is treated with ethyl iodide, and assuming that the reaction takes place through the intermediate stage of the O-alkyl ethers, then ketene-acetal, $\text{ROOCCH} = \text{C}(\text{OCH}_3)\text{OC}_2\text{H}_5$, should be produced in both cases. If the reaction product is hydrolysed, and the alcohol is distilled off, the alkylation product obtained with methyl iodide should yield methyl alcohol, and that with ethyl iodide, ethyl alcohol. In neither of the two cases, however, can the introduced alkyl group be detected. This speaks against the reaction taking place through the O-ethers.

A simple monomolecular anhydride of malonic acid is not known. If the acid itself, or its esters are heated with phosphorus pentoxide, carbon suboxide is formed (see p. 181). Malonyl chloride, $\text{ClCOCH}_2\text{COCl}$, is easily obtained by the action of thionyl chloride on the acid. In cyanacetic ester, CNCH_2COOR , (the semi-nitrile of malonic ester), the methylene group has a similar reactivity to that in malonic acid itself; this compound is therefore often used for preparative work.

The ureide of malonic acid, *barbituric acid*, is of great interest. Many syntheses are available for it and its C-alkyl derivatives. It is usually made by the condensation of malonyl chloride or malonic ester with urea:



Barbituric acid crystallizes beautifully, is not very soluble in water, and reacts strongly acid. The reactivity of the methylene group of the malonic acid still persists in this compound. By the action of nitric acid a hydrogen atom can be replaced by the nitro-group, the nitrobarbituric acid thus obtained can be reduced to aminobarbituric acid (*uramil*), and this can be converted by the action of potassium cyanate into ureido-barbituric acid, or *pseudo-uric acid*:

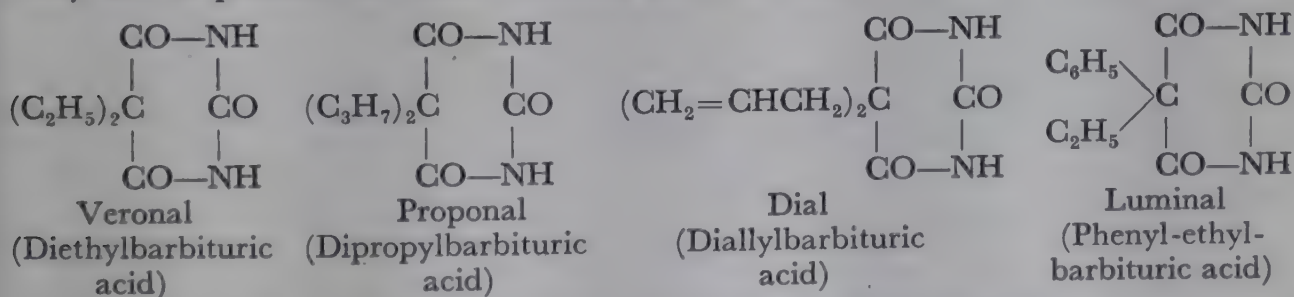


All these compounds are intermediate stages in a synthesis of uric acid (see Ch. 62).

Isonitrosobarbituric acid or *violuric acid*, $\text{HON}=\text{C} \begin{array}{c} \text{CO}-\text{NH} \\ \diagup \quad \diagdown \\ \text{CO}-\text{NH} \end{array} \text{CO}$, has

also aroused great interest. It is obtained by nitrosylation of barbituric acid, or from alloxan (see Ch. 62) and hydroxylamine and is characterized by the beautiful colours of its salts. Thus a blue and a red potassium salt, a red and a dark yellow lithium salt, etc. are known.

The *C-dialkylbarbituric acids* have become of practical importance, as they include a series of very useful hypnotics (the veronal group), particularly *veronal* or diethylbarbituric acid (E. Fischer, v. Mering), *proponal*, *dial*, *luminal*, etc. They are at present the most effective and the most commonly used hypnotics:

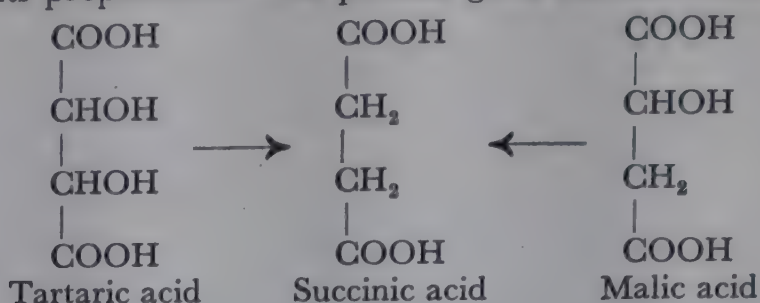


Evipan, the sodium salt of N-methyl-C-methyl-C-cyclohexyl-barbituric acid, is often used as an anæsthetic.

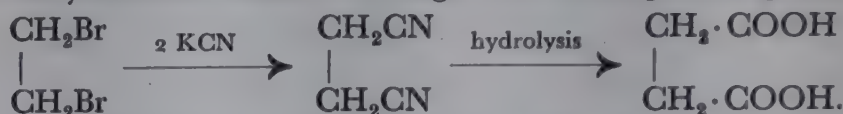
Succinic acid, $\text{HOOCCH}_2\text{CH}_2\text{COOH}$. The name of this acid is derived from its occurrence in amber, (*succinum* = amber). It is also present in many plants (e.g. in unripe gooseberries, grapes, beet-juice, and rhubarb), in lignite and fossil woods, and it is formed in large quantities by certain bacterial decompositions of malic acid and tartaric acid, and the fermentation of proteins (e.g. casein). Its occurrence in alcoholic fermentation is important; it apparently arises

from glutamic acid (a protein amino-acid). It is said to be contained in the thymus and thyroid glands of some animals.

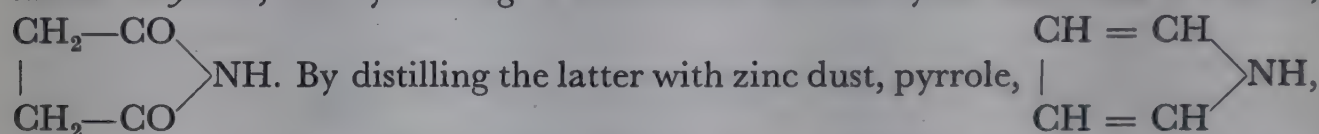
The fermentation of ammonium tartrate or calcium malate with moulds is chiefly used for its preparation. The process gives succinic acid of a high degree of purity:



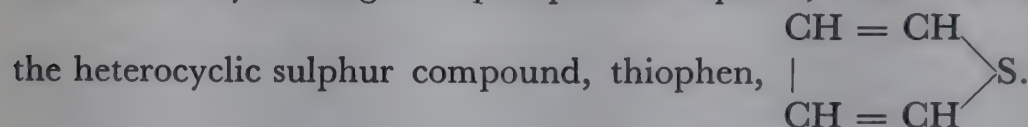
Succinic acid is also obtained as a by-product in the distillation of amber waste in the preparation of colophony. Synthetically, it is most conveniently obtained from ethylene dibromide through the corresponding dicyanide:



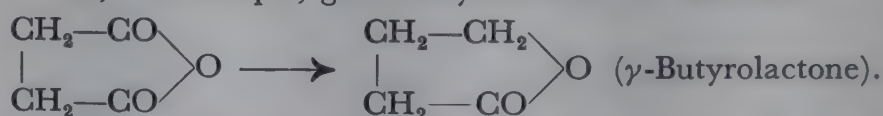
Succinic acid crystallizes well, and melts at 183° . It has a strong tendency to form closed-ring derivatives. Thus, on distillation it is converted into the cyclic *succinic anhydride*, and by heating its ammonium salt the cyclic *succinimide* is formed,



is obtained. By heating with phosphorus sulphide, succinic acid is converted into

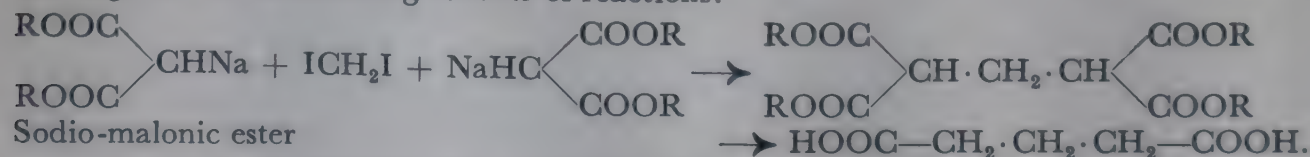


Succinyl chloride, $\text{ClCO}(\text{CH}_2)_2\text{COCl}$, and succinic anhydride are used in various syntheses. The latter, for example, gives butyrolactone on reduction:



Several dyes [e.g. Rhodamine S (see Ch. 49, sec. F, subsec. (c))] are obtained with the aid of succinic anhydride. The mercury compound of succinimide is used in medicine as a mercury preparation. Crude succinic acid (from amber) finds a small use in medicine.

Glutaric acid, $\text{HOOC}(\text{CH}_2)_3\text{COOH}$. This substance occurs in beet-juice and in the wash water from raw sheep's wool. Of the many methods of preparing this substance, one is given in the following scheme of reactions:

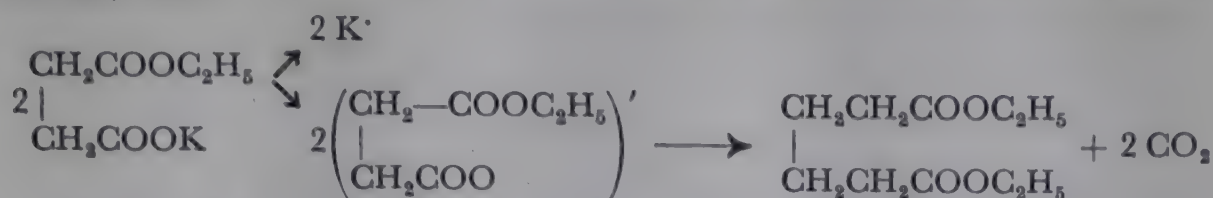


Adipic acid, $\text{HOOC}(\text{CH}_2)_4\text{COOH}$. This compound is also found in beet-juice. It is formed by the oxidation of fats and castor oil, but particularly from Russian mineral oils, which are rich in *cyclohexane*. The oxidation of *cyclohexanol* and *cyclohexanone* to adipic acid proceeds even more readily:



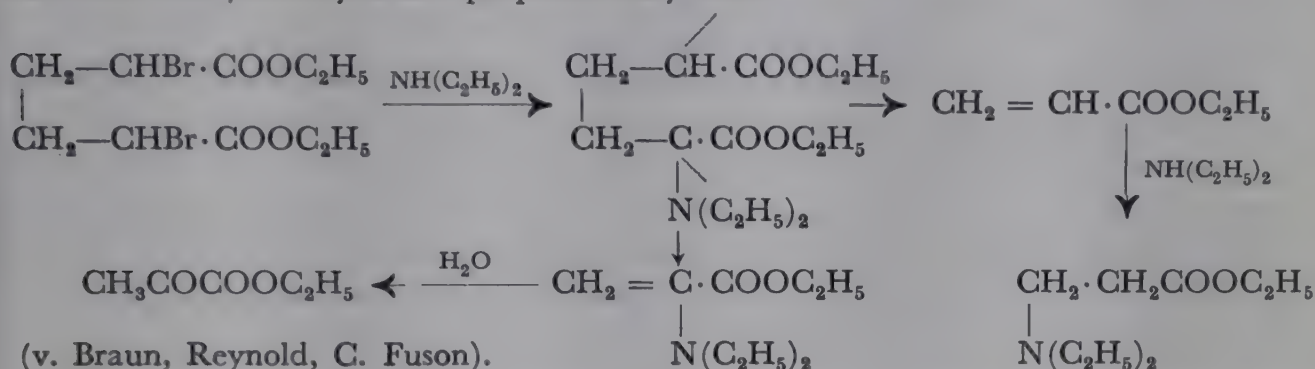
The oxidation may be carried out with 65 per cent nitric acid at $20-30^\circ$.

Another method of formation is the electrolysis of potassium ethyl succinate. The reaction corresponds completely to Kolbe's synthesis of hydrocarbons from the alkali salts of the fatty acids:



Adipic acid has recently found some technical application, e.g. as a substitute for tartaric acid in the manufacture of baking powders and mineral waters, and certain of its esters are used as gelatinizing agents. Its most important use, however, is in the manufacture of a new synthetic fibre, "*Nylon*". This fibre which is extraordinarily strong, elastic, and of great tensile strength, is produced by E. I. du Pont de Nemours (U.S.A.) from a polyamide, prepared by fusion of hexamethylenediamine with adipic acid.

An interesting decomposition, particularly in connection with the cleavage occurring in the alcoholic fermentation of sugars containing also six carbon atoms, is shown by the action of diethylamine on α, α' -dibromo-adipic diethyl ester. It is broken down into pyruvic acid ester and β -diethylamino-propionic ethyl ester:



Pimelic acid, $\text{HOOC}(\text{CH}_2)_5\text{COOH}$. This substance can be obtained from castor oil, or from pentamethylene chloride through the dinitrile. It occurs in the urine of herbivorous animals. For the reductive cleavage of salicylic acid to pimelic acid, see Ch. 41.

Suberic acid, $\text{HOOC}(\text{CH}_2)_6\text{COOH}$, is obtained by the action of nitric acid on cork (*suber*=cork), or castor oil. It can be obtained synthetically by electrolysis of the potassium salt of glutaric acid ester.

Azelaic acid, $\text{HOOC}(\text{CH}_2)_7\text{COOH}$. This acid is also formed by the oxidation of castor oil, best with potassium permanganate. It is also produced fairly smoothly by ozonization of oleic acid (see p. 207).

Sebacic acid, $\text{HOOC}(\text{CH}_2)_8\text{COOH}$. This acid is usually prepared by the dry distillation of the sodium soap obtained by alkaline fission of castor oil.

Higher dicarboxylic acids and hydroxy-derivatives of higher dicarboxylic acids have been found in cork, e.g. eicosane-dicarboxylic acid, $\text{HOOC} \cdot \text{C}_{20}\text{H}_{40} \cdot \text{COOH}$, and phloionic acid, $\text{HOOC}(\text{CH}_2)_7\text{CHOHCHOH}(\text{CH}_2)_7\text{COOH}$.

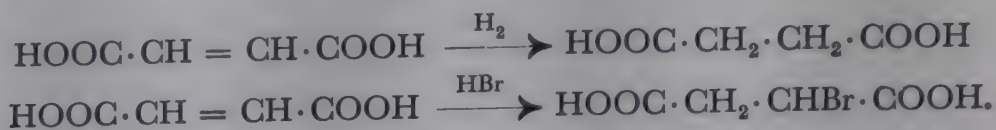
IV. Unsaturated dicarboxylic acids

The most important unsaturated dicarboxylic acids are β -dicarboxylic acids, the first members of which, *maleic acid* and *fumaric acid*, have been specially considered and investigated for stereochemical reasons.

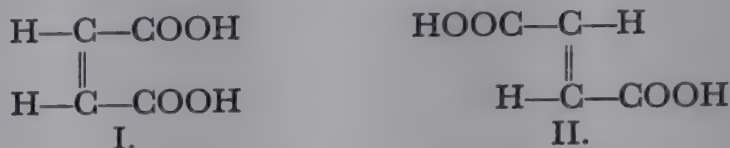
Maleic acid and **fumaric acid**. $\text{HOOC} \cdot \text{CH} = \text{CH} \cdot \text{COOH}$. Both these acids are obtained by heating malic acid, fumaric acid in greater yield at lower temperatures and maleic acid at higher temperatures. The reaction is simply elimination of water from malic acid:



On the other hand, both maleic and fumaric acid can be hydrated again by heating with water in a sealed tube, giving DL-malic acid. On reduction they both give succinic acid, and both add on HBr to give the same bromosuccinic acid:



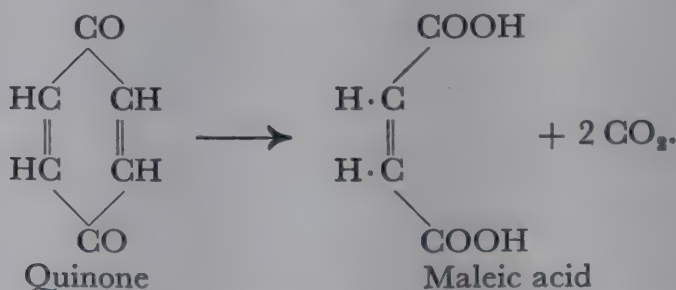
These reactions show that maleic and fumaric acid possess the same structure, so that their differences must depend on the spatial arrangement of the molecule. Theory predicts that, as they are ethylenic compounds of the type $\text{XHC}=\text{CHX}$ (cf. p. 48), there should be two possible stereo-formulae:



of which one must represent maleic acid, and the other fumaric acid. The assignment of these two formulae to the two acids offers in this case no difficulty. Maleic acid forms an anhydride very easily, while fumaric acid does not. If the latter is distilled it is converted with rearrangement into maleic anhydride. The formation of an anhydride will obviously be favoured by a *cis*-arrangement of the carboxyl groups, so that maleic acid is assigned the *cis*-configuration (I), and fumaric acid the *trans*-configuration (II) (van 't Hoff, Le Bel, J. Wislicenus):



The *cis*-configuration of maleic acid is supported by a remarkable, simple method of formation of this compound. If quinone is oxidized by a sulphuric acid solution of silver sulphate and alkali persulphate, maleic acid is obtained in good yield. Since the carbonyl groups of the quinone are arranged in the *cis*-position with respect to the double bonds, it is very probable that this is also the case for the carboxyl groups of the oxidation product, maleic acid:



However, some fumaric acid is formed at the same time, probably owing to the isomerization of the labile maleic acid into the more stable fumaric acid.

The geometrical isomerism of ethylenic compounds has not been studied so thoroughly for any other pair of ethylenic derivatives as for maleic and fumaric acid. On the other hand there were formerly few other cases where the assignment of the two possible space formulae to the isomers was as little in doubt as here. It thus became common to call *cis*-ethylenic compounds, *malenoid*, and *trans*-ethylenic derivatives, *fumaroid* forms.

Some of the physical and chemical properties of the two stereoisomeric acids

are to a certain extent different. Maleic acid melts at 130°, fumaric acid at 287°. The former is very readily soluble in water, and is precipitated on adding baryta water; the latter is difficultly soluble in water, and is not precipitated by baryta.

Maleic acid is a stronger acid than its isomeride. The constants for the primary dissociation are:

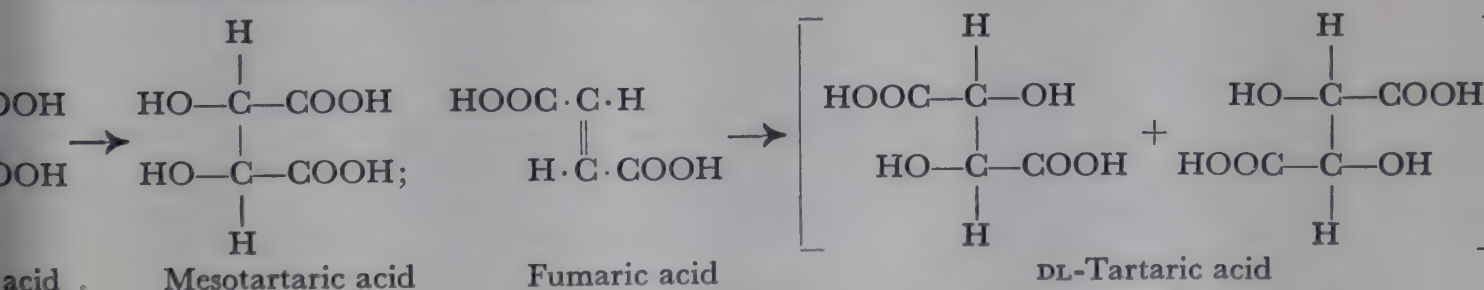
maleic acid	1.170
fumaric acid	0.093.

On the other hand, the hydrogen atom of the second carboxyl group of fumaric acid dissociates more easily than that of maleic acid (Ostwald).

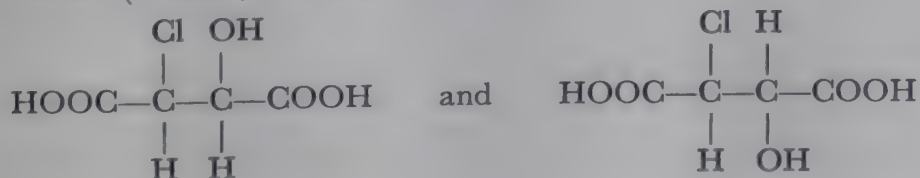
Of the two stereoisomeric acids, fumaric is the more stable. This can readily be understood from its configuration. Since groups with similar electric charges always tend to repel each other, that form will be the more stable in which the two negative carboxyl groups are as far apart from each other as possible, i.e. the *trans*-form, fumaric acid.

A number of physical and chemical effects can bring about the rearrangement of maleic acid into fumaric acid, such as exposure to light, heating to the melting point, nitrous acid, and concentrated halogen hydracids. Iodine, mercuric chloride with a trace of potassium persulphate, and primary and secondary amines are particularly effective in isomerizing maleic acid esters. On the other hand it is also possible by adding energy, e.g. by exposure to ultra-violet light, to reconvert the more stable fumaric acid at least partially into the energy-rich maleic acid (Stoermer). The dinitrile of fumaric acid is converted to a considerable extent into the dinitrile of maleic acid by the action of hydrogen chloride in ether.

Much consideration has been given to the question of how the addition of two groups of atoms to *cis-trans* isomerides of the maleic-fumaric acid type takes place. There is the possibility that addition will take place in the *cis*- or in the *trans*-position. Maleic acid is oxidized by potassium permanganate to mesotartaric acid (see p. 317), whilst fumaric acid gives racemic acid (see p. 318). Since mesotartaric acid contains the two hydroxyl groups in the *cis*-position, their addition to maleic acid must have taken place in the *cis*-position. In racemic acid, on the other hand, the OH groups are in the *trans*-position, so that addition to fumaric acid takes place in the *trans*-position (Kekulé, McKenzie):



This course, however, is by no means the case for all addition reactions in which maleic and fumaric acids take part. Thus, hypochlorous acid adds on to maleic acid to give one homogeneous chloromalic acid. Under the same conditions, however, fumaric acid gives a mixture of the two possible isomeric chloromalic acids (Lossen, R. Kuhn):



The two chloromalic acids have been resolved into their optically active forms.

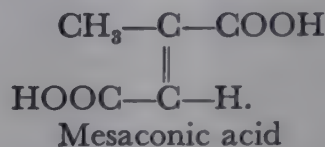
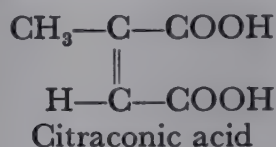
The catalytic reduction of *cis*-ethylenic compounds proceeds more rapidly than in the case of the *trans*-isomerides (C. Paal). Thus,

<i>isocrotonic acid</i>	is more easily reduced than	<i>crotonic acid</i>
<i>erucic acid</i>	„ „ „ „ „	<i>brassicic acid</i>
<i>coumarinic acid</i>	„ „ „ „ „	<i>o-coumaric acid</i>
<i>isostilbene</i>	„ „ „ „ „	<i>stilbene</i> .

NATURAL OCCURRENCE. Fumaric acid is often found in mushrooms (*Boletus* and *Agaricus* species), also in the lichen *Cetraria islandica*, in *Fumaria officinalis* (fumitory), and in other plants. Its name is derived from *Fumaria*. It can be formed from sugar by the action of moulds (F. Ehrlich) and appears to be a normal product of animal metabolism.

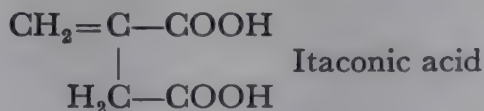
Maleic acid, on the other hand, does not occur naturally.

Citraconic acid, mesaconic acid, itaconic acid. In the same isomeric relationship as maleic and fumaric acids stand *citraconic acid* and *mesaconic acid*. The first of these is assigned the *cis*-structure on the basis of the ease with which it forms an anhydride. Mesaconic acid cannot form an anhydride:

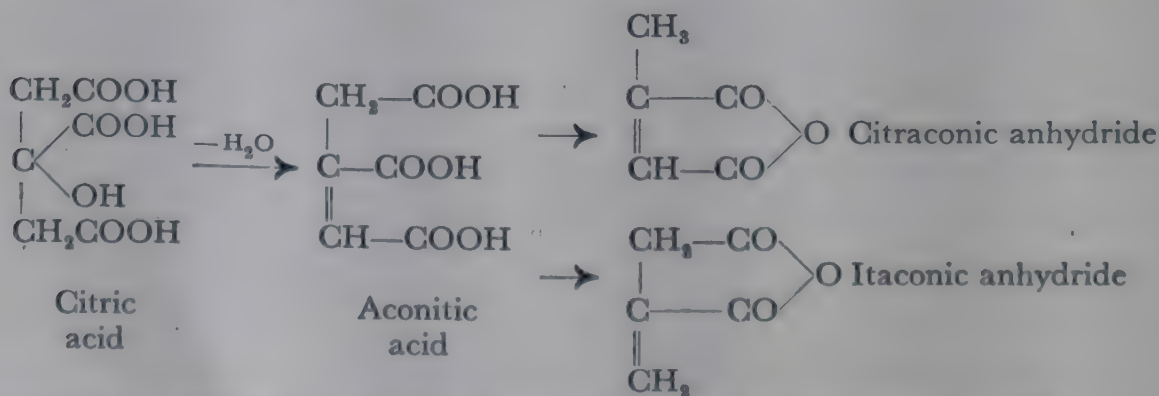


Citraconic acid is methylmaleic acid, and mesaconic acid is methylfumaric acid.

A third, isomeric, unsaturated dicarboxylic acid, *itaconic acid*, or methylene-succinic acid, belongs to the series:



Citric acid is the starting substance from which all three acids may be prepared. By rapid distillation it gives the anhydrides of itaconic acid and citraconic acid according to the way in which carbon dioxide is eliminated. The former is converted by repeated distillation, to a large extent into citraconic anhydride, from which, by heating with water at 150°, much itaconic acid is obtained, or, by boiling with alkali, mesaconic acid. An intermediate product in the decomposition of citric acid is *aconitic acid*:



Citraconic acid melts at 91°, mesaconic acid at 202°, and itaconic acid at 161°.

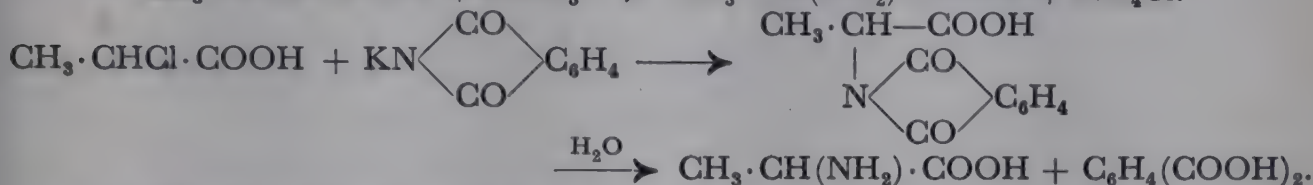
CHAPTER 18

AMINOCARBOXYLIC ACIDS AND PROTEINS

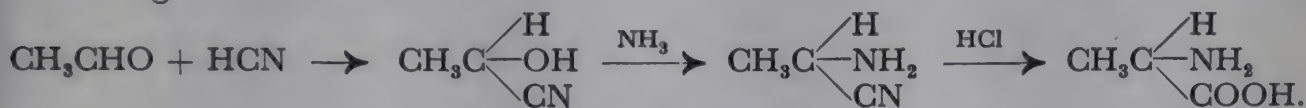
I. Aminocarboxylic acids¹

With the consideration of the aminocarboxylic acids, commonly known as *amino-acids*, we enter a branch of the subject which is equally interesting both from the purely chemical and the physiological aspects. The amino-acids, or to be more precise the α -amino-acids exclusively, are the building stones of the proteins, from which they are produced by hydrolysis.

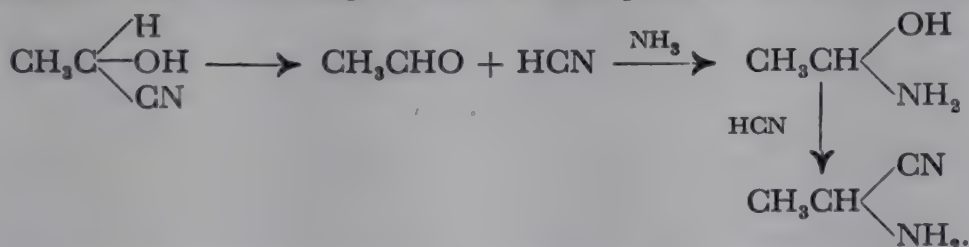
OCCURRENCE AND METHODS OF PREPARATION. 1. For the synthesis of amino-acids, the action of ammonia on the halogen-substituted fatty acids, or the action of potassium phthalimide on these compounds, is frequently chosen. In the latter case the process is completed by acid hydrolysis to remove the phthalic acid radical:



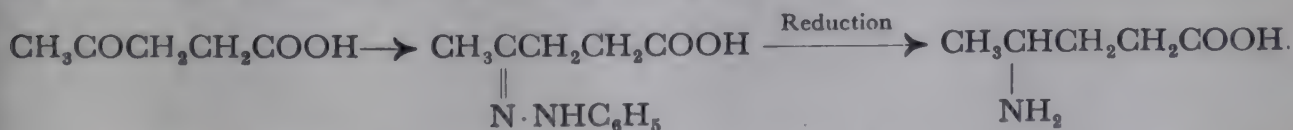
2. The synthesis due to Strecker is often used. It starts with the cyanhydrins, converts these into aminonitriles by means of ammonia, and then hydrolyses these to give amino-acids:



Cocker, Lapworth, and Peters interpret the course of the Strecker synthesis in a somewhat different way. According to them it takes place in the following stages:

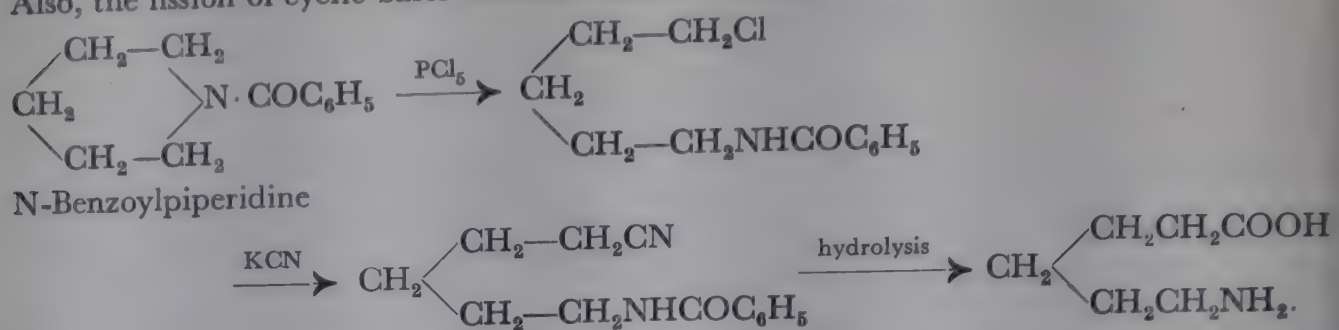


3. In addition to these general methods of preparation there are several others which are occasionally used, but are of secondary interest for preparative purposes. Amino-acids can, for example, be obtained from keto-acids through the hydrazones:

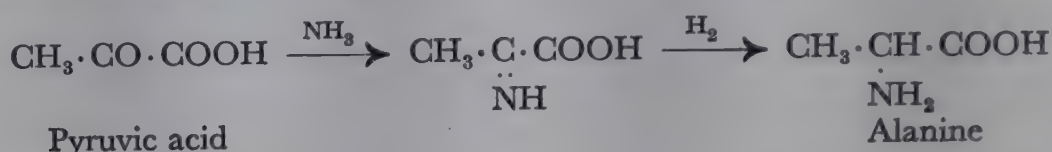


¹ See EMIL FISCHER, *Untersuchungen über Aminosäuren, Polypeptide und Proteine*, vol. I, Berlin, (1906), vol. II, Berlin, (1923). — H. G. BENNETT, *Animal Proteins*, London, (1921). — TH. B. OSBORNE, *The vegetable Proteins*, 2nd ed., London, (1924). — H. H. MITCHELL and T. S. HAMILTON, *The Biochemistry of the Amino-Acids*, New York, (1929). — G. TH. PHILIPPI, *On the Nature of Proteins*, Amsterdam, (1936). — DOROTHY JORDAN LLOYD, *Chemistry of the Proteins*, 2nd ed., Philadelphia, (1938). — D. J. LLOYD and A. SHORE, *Chemistry of the Proteins and its Economic Applications*, 2nd ed., London, (1938). — C. L. A. SCHMIDT, *The Chemistry of the amino-acids and proteins*, 2nd ed., London, (1943). — E. J. COHN and J. T. EDSALL, *Proteins, Amino Acids and Peptides as Ions and Dipolar Ions*, New York, (1944). — M. SAHYUM, *Outline of the Amino Acids and Proteins*, New York and London, (1945).

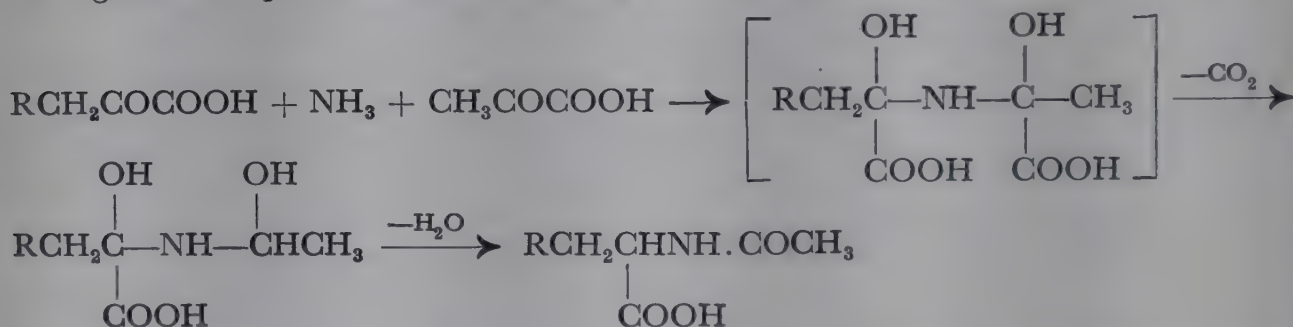
Occasionally the addition of ammonia to unsaturated carboxylic acids is successful. Also, the fission of cyclic bases has been used to obtain certain amino-acids:



4. The discovery of Knoop that amino-acids can be obtained by the catalytic reduction of mixtures of keto-acids and ammonia (or other amines) is important in connection with the problem of the formation of amino-acids in the organism. As a reducing agent, in addition to catalytically activated hydrogen, cysteine (q.v.), for example, a normal constituent of proteins, may also be used. Iminocarboxylic acids are assumed to be intermediate products in the reaction:

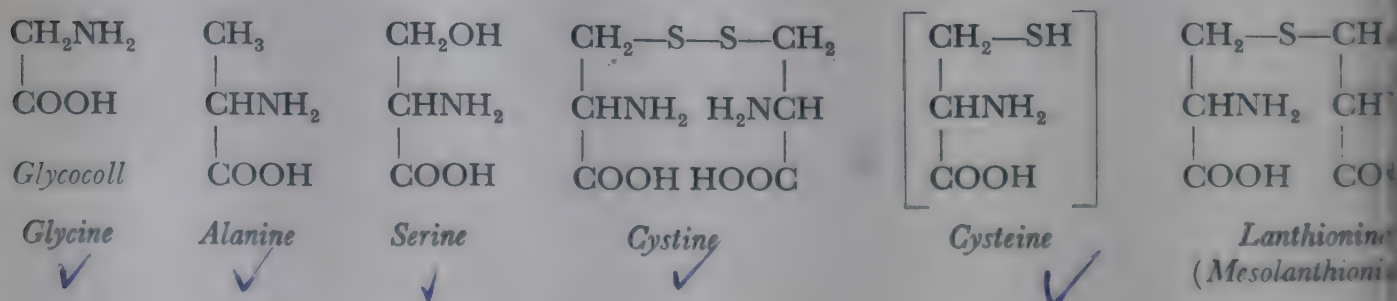


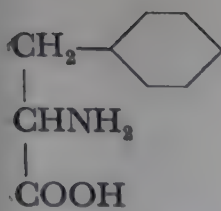
The *biological* synthesis of the amino-acids from keto-acids probably follows a somewhat more complicated course, and often proceeds via the N-acetyl derivatives of the amino-acids, apparently through the participation of pyruvic acid in the synthesis. Vincent du Vigneaud has put forward the following scheme for these reactions:



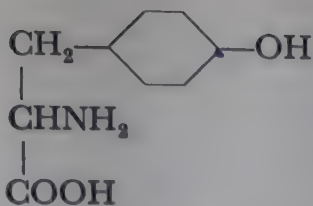
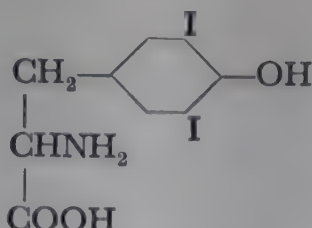
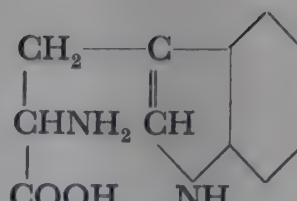
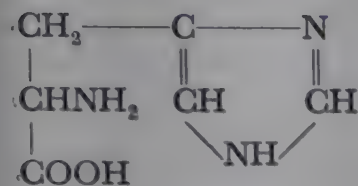
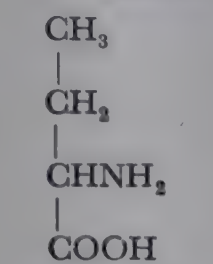
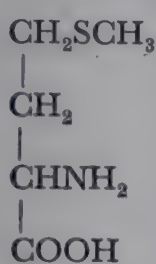
About twenty-five different α -amino-acids are formed, as mentioned above, by the hydrolysis of proteins. They are contained in proteins in very different quantities. The hydrolysis is usually carried out by boiling with hydrochloric or sulphuric acid. Alkalis are also effective, but the hydrolysis in this case is less smooth, and is always accompanied by considerable racemization of the amino-acids. Most proteins may, however, be decomposed by enzymes (trypsin, pepsin). Pepsin is most active in weakly acid solution (pH about 3–3.5), trypsin in weakly alkaline solution (pH about 8).

The following list gives the amino-acids which have so far been isolated from proteins:

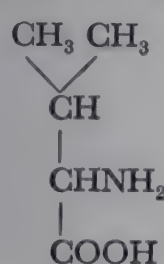
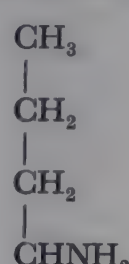




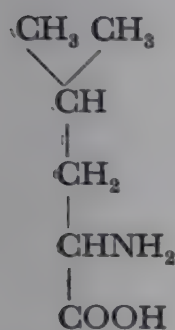
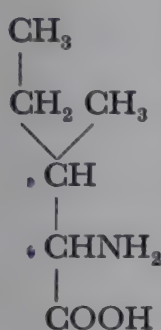
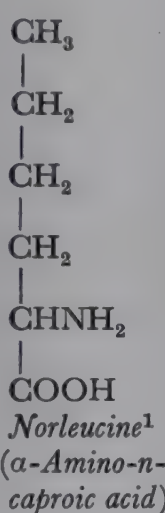
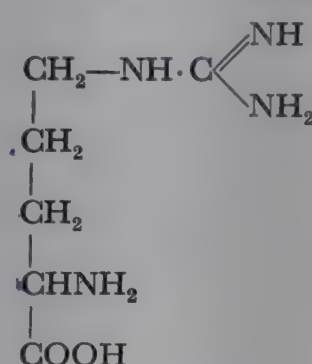
Phenylalanine ✓

Tyrosine
p-Hydroxyphenylalanine ✓Diiodotyrosine
(Iodogorgoic acid)Tryptophan
(β -Indolylalanine) ✓Histidine
(β -Imidazolylalanine) ✓ α -Aminobutyric acid¹

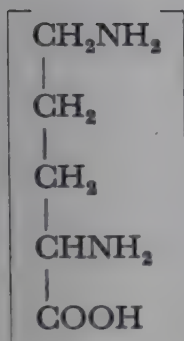
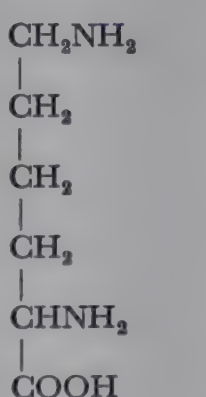
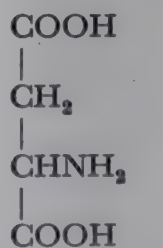
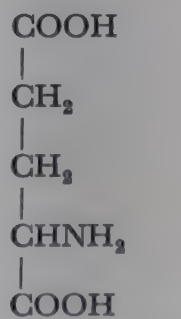
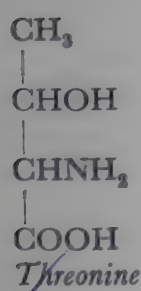
Methionine

Valine (α -Amino-
isovaleric acid) ✓

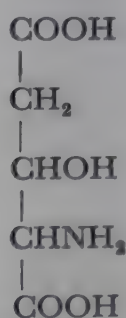
Norvaline

Leucine
(α -Aminoisocaproic acid)Isoleucine
(α -Amino- β -methyl-
valeric acid) ✓Norleucine¹
(α -Amino-*n*-
caproic acid)

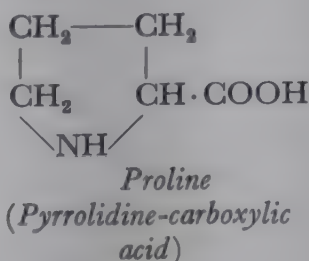
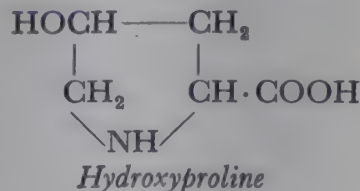
Arginine ✓

Ornithine
(α, δ -Diaminovaleric acid)Lysine
(α, ϵ -Diaminocaproic acid)Aspartic acid
(Aminosuccinic acid) ✓Glutamic acid
(α -Aminoglutaric acid) ✓

Threonine ✓



Hydroxyglutamic acid

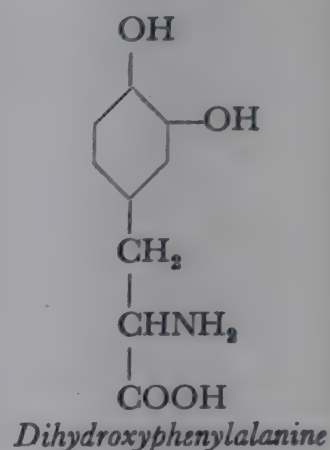
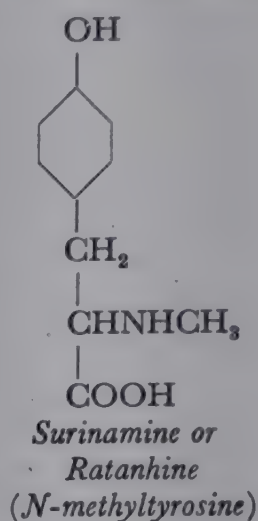
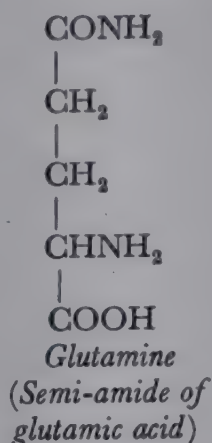
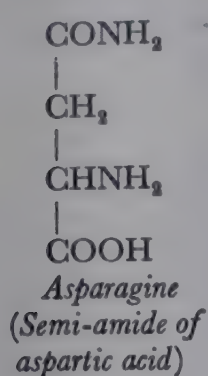
Proline
(Pyrrolidine-carboxylic acid)

Hydroxyproline

¹ Only rarely met with in proteins (Abderhalden).

Cysteine which occurs in proteins, is converted, when isolated, into cystine by atmospheric oxidation. Ornithine arises from arginine by hydrolysis. A *serine phosphate* occurs in phospho-proteins (casein, vitellin, etc.).

In plants the following substances, which bear a close relationship to the protein amino-acids are often met with; of these asparagine and glutamine can also be obtained from proteins by enzymic hydrolysis:



Two different methods are available for the separation of the amino-acids, which is not an easy operation. In E. Fisher's method, the mixture of amino-acids is first esterified with alcohol and hydrogen chloride, and the free amino-acid esters are obtained from the ester hydrochlorides by the action of alkali. These are then separated by fractional distillation. Dakin extracts the hydrolysed protein with butyl alcohol, which extracts chiefly the monoamino-acids. The diamino-acids and dicarboxylic acids, which are insoluble in butyl alcohol are thus conveniently separated. For the separation of some individual amino-acids, or groups of amino-acids, special procedures have, moreover, been developed, e.g. the basic amino-acids (arginine, lysine, histidine) are precipitated by phosphotungstic acid; tyrosine and cystine which are difficultly soluble in water are usually isolated by

	Casein	Serum Albumin (from cattle)	Edestin
	%	%	%
Arginine	3.78	6.2	17.4
Aspartic acid	7.4	11.1	13.4
Glutamic acid	21.7	16.6	19.4
Histidine	3.0	3.7	2.61
Isoleucine	7.6	2.97	6.47
Leucine	10.25	11.8	7.5
Lysine	8.07	10.3	2.09
Methionine	2.69	0.86	2.07
Phenylalanine	5.45	6.48	5.22
Proline	11.6	5.1	4.6
Threonine	4.28	6.2	3.7
Tyrosine	6.2	4.3	3.7
Valine	7.15	6.6	6.6
Tryptophan	1.28	0.41	0.86
Total	100.45	92.62	95.62

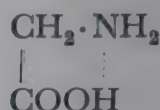
Naturally occurring amino-acids	m.p. or decomp. temp.	$[\alpha]_D$	Solubility in water
Glycocoll	289–292°	inactive	readily soluble
L(+)-Alanine	297°	+ 2.7°	readily soluble
L(—)-Serine	228°	— 6.8°	readily soluble
L(—)-Methionine	280°	— 8.2	fairly readily soluble
L(+)-Aminobutyric acid	302°	+ 5.1°	readily soluble
L(—)-Cystine	258–261° (decomp.)	—222.4° (in HCl solution)	almost insoluble in cold H ₂ O
Mesolanthionine	304°	inactive	
L(+)-Valine	315°	+ 6.42°	fairly readily soluble
L(+)-Norleucine	285°	+ 23.1° (in 20 % HCl)	1.7:100 (23°)
L(—)-Leucine	337°	— 10.4°	1:45 (20°)
L(+)-Isoleucine	280°	+ 9.7°	1:25.8 (15.5°)
L(—)-Phenylalanine	about 278°	— 35.3°	1:32.4 (25°)
L(—)-Tyrosine	342–344°	— 8.6°	1:2491 (17°)
L(—)-Dihydroxyphenyl- alanine	280° (decomp.)	(in 21 % HCl) — 14.28° (in N HCl)	1:200 (cold water)
L(—)-Tryptophan	about 289°	—30° to —34°	difficultly sol. in cold water, readily sol. in hot
L(—)-Histidine	about 277°	— 39.7°	readily soluble
L(+)-Arginine	238° (decomp.)	+ 26.5°	readily soluble
L(+)-Ornithine	Syrup	+ 16.8° (hydrochloride)	readily soluble
L(+)-Lysine	224°	+ 15.3° (hydrochloride)	readily soluble
L(—)-Aspartic acid	251°	+6° (21.5°) at higher temps. lævorotatory	1:222 (20°)
L(—)-Asparagine	226–227°	— 5.4°	3.1:100 (28°)
L(+)-Glutamic acid	248°	+ 12.0°	1:100 (16°)
L(+)-Glutamine	?	+ 6.45°	1:27.7 (18°)
Hydroxyglutamic acid	130–135°	slightly dextro- rotatory	readily soluble
L(—)-Threonine	257°	—	readily soluble
L(—)-Proline	215–220°	— 81.9°	readily soluble
L(—)-Hydroxyproline	about 270°	— 80.0°	readily soluble

fractional crystallization, etc. The amounts of the different amino-acids in proteins vary from protein to protein. (The first of the two tables above gives the isolated constituents of three different proteins).

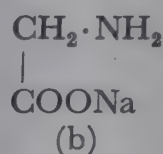
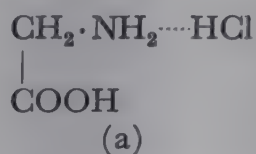
PROPERTIES: The α -amino-acids are all crystalline solids. They vary considerably as regards solubility in water, and specific rotation (see table above). They are usually insoluble in alcohol though there are exceptions (proline). Some of them have a sweet taste (glycocoll, D-alanine, serine, D-asparagine, phenylalanine, etc.).

Aqueous solutions of amino-acids which contain only *one* basic group, (NH₂), and *one* carboxyl group, react approximately *neutral*. The reason for this is that

the amino-acids form internal salts. The amino- and carboxyl-radicals saturate themselves *intramolecularly*, just as an amine is neutralized extramolecularly by a carboxylic acid:

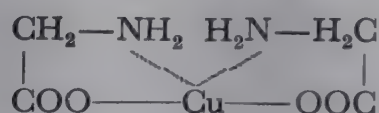


With mineral acids and strong alkalis amino-acids form salts. The salts of the former are of the type (a) and react acid; those of the latter correspond to formula (b) and are bases:



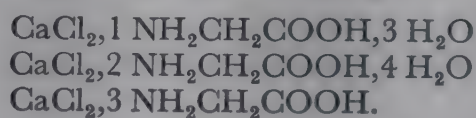
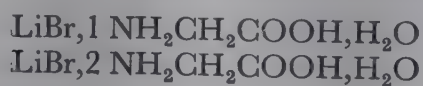
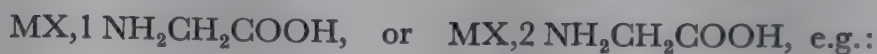
The amino-acids are thus amphoteric substances, and possess the properties of buffers. They may therefore be used for the preparation of solutions of known hydrogen ion concentration.

The *copper salts of the amino-acids* are distinguished by their splendid blue colour. Investigation has shown that they are internal complexes of the type:



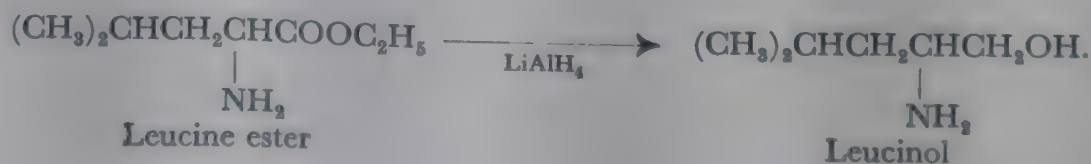
They are not decomposed by alkalis, although hydrogen sulphide precipitates copper sulphide. Since these copper salts usually crystallize well, and are often difficultly soluble, they are very useful for the isolation and purification of the amino-acids.

Many amino-acids are capable of forming well-crystallized molecular compounds with metal salts. P. Pfeiffer has prepared a large number of these double salts, mostly of the type

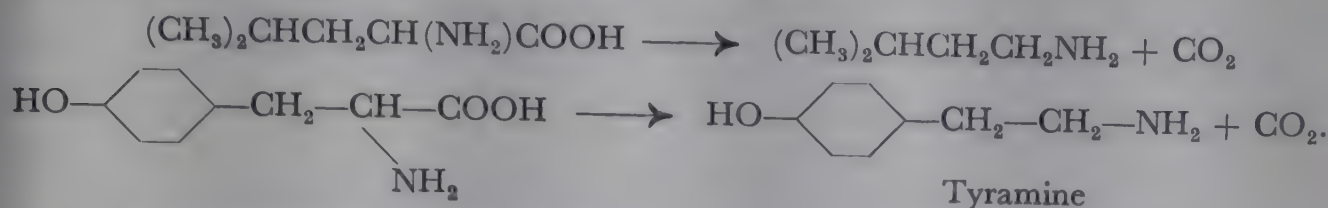


Their differing solubilities makes it occasionally possible to use them for the separation of amino-acids. They are of particular interest, however, because they furnish the key to the understanding of the behaviour of proteins towards neutral salts, some proteins being precipitated by solutions of such metal salts, and others not.

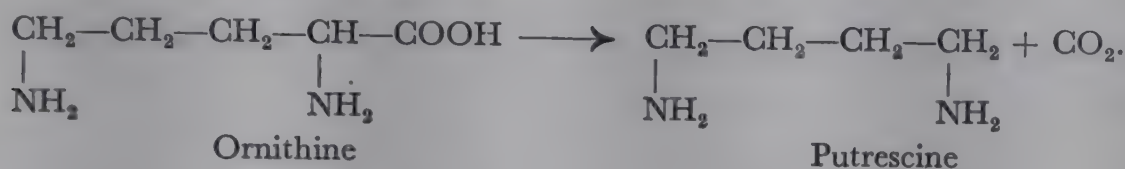
The chemical reactions of the amino-acids are determined on the one hand by the amino-group, and on the other by the carboxyl group. They can, for example, be converted into N-acyl derivatives, and on the other hand into esters of the amino-acids. The latter can be reduced to amino-alcohols, homologues and derivatives of colamine (q.v.), by the action of sodium and alcohol or with lithium-aluminium hydride:



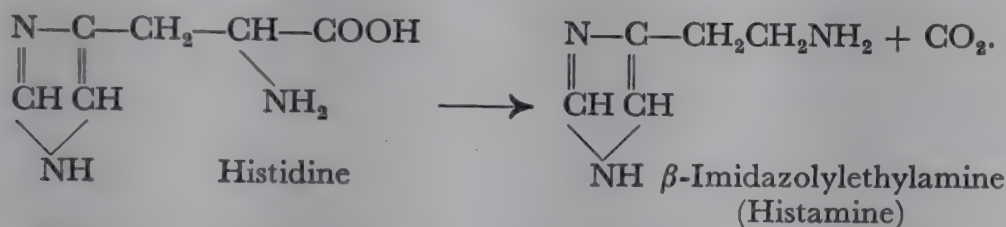
Several amino-acids on careful heating, particularly in indifferent high-boiling solvents, lose carbon dioxide, and give amines. Thus leucine gives *isoamylamine*, tyrosine gives *tyramine* (B. H. Waser, Zemplén):



The same process may also take place under the influence of bacteria and in animal tissue by the action of an amino-acid carboxylase. Many species of bacteria (e.g. *B. proteus*, *B. coli*, *B. subtilis*) break down amino-acids by decarboxylation to amines. Such processes always take place in the putrefaction of proteins, and the bases, *putrescine* and *cadaverine* (p. 251) owe their formation in decaying proteins to this reaction. The parent substance of putrescine is ornithine (arginine), and that of cadaverine is lysine:



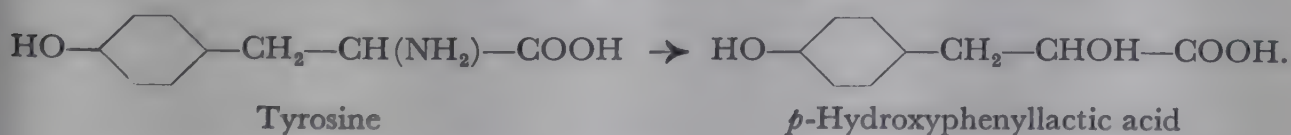
Some of these "*proteinogenic amines*"¹ have medicinal use on account of their effect on the blood pressure (causing it either to increase or decrease) and their uterus-contracting properties. Thus β -imidazolyethylamine, which, for example, is obtained technically from histidine by bacterial putrefaction, and *p*-hydroxyphenylethylamine (tyramine, uteramine) are used for these purposes:



The N-dimethyl-derivative of tyramine, known as *hordenine*, is found in the embryo of barley and in a species of cactus (*Anhalonium*):



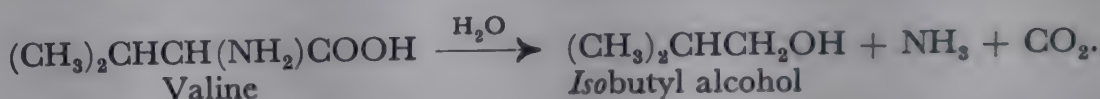
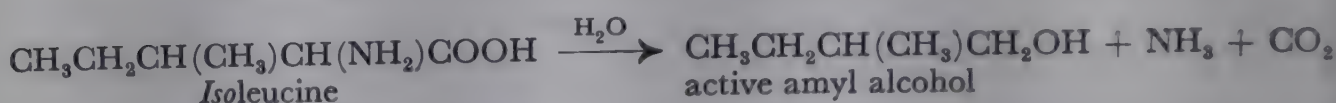
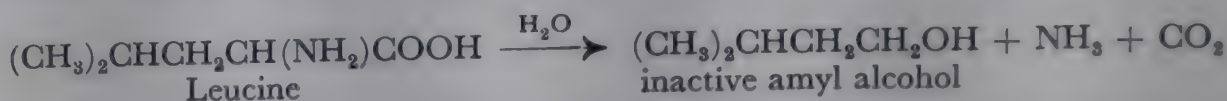
For the formation of proteinogenic amines by bacterial decomposition of proteins a weakly acid medium is favourable. If an alkaline medium (pH = 7.7) is used, the same bacilli produce hydroxy-acids. For example, tyrosine gives *p*-hydroxyphenyllactic acid, and tryptophan gives indolelactic acid:



Here, then, is a second natural degradation of amino-acids.

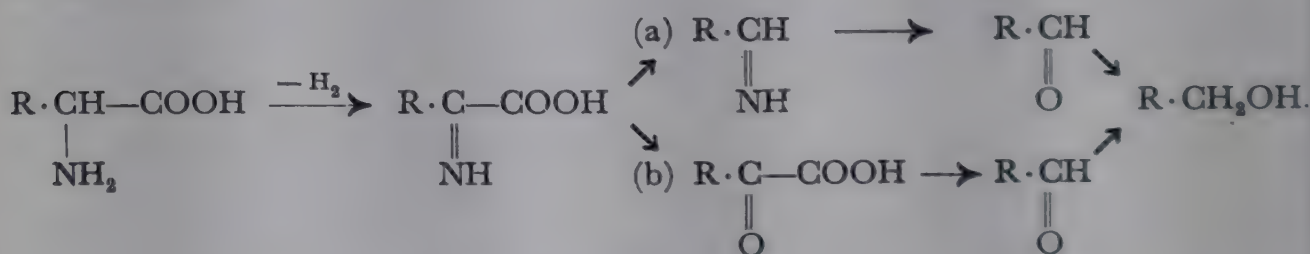
¹ See G. BARGER, *The Simpler Natural Bases*, London, (1914). — M. GUGGENHEIM, *Die biogenen Amine*, III, Ed. Basel, (1940). — P. HIRSCH, *Einwirkung von Mikroorganismen auf die Eiweisskörper* (1918). — H. H. MITCHELL and T. S. HAMILTON, *Biochemistry of the Amino-acids*, New York (1929).

In a third type of decomposition, these substances are acted upon by certain micro-organisms, e.g. yeast (Felix Ehrlich). In alcoholic fermentation, various higher alcohols (amyl and butyl alcohols) are formed, as has already been mentioned, which owe their origin to an "amino-acid fermentation". Inactive fermentation amyl alcohol arises from leucine, the optically active form from *isoleucine*, and *isobutyl* alcohol from valine:

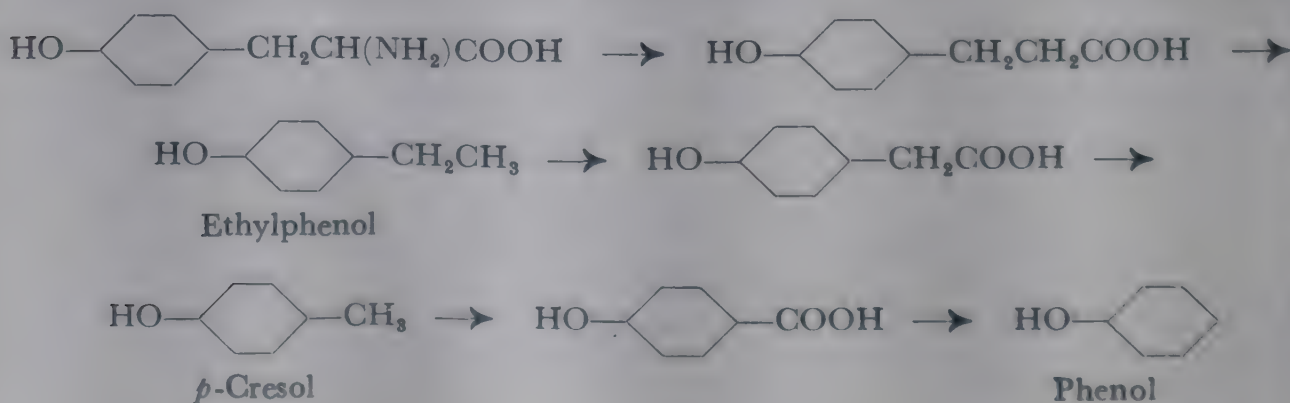


Succinic acid, which is always found in the fermented liquid, probably arises in a similar way from glutamic acid, since addition of some of the latter to the sugar before fermentation causes an increase in the amount of succinic acid formed.

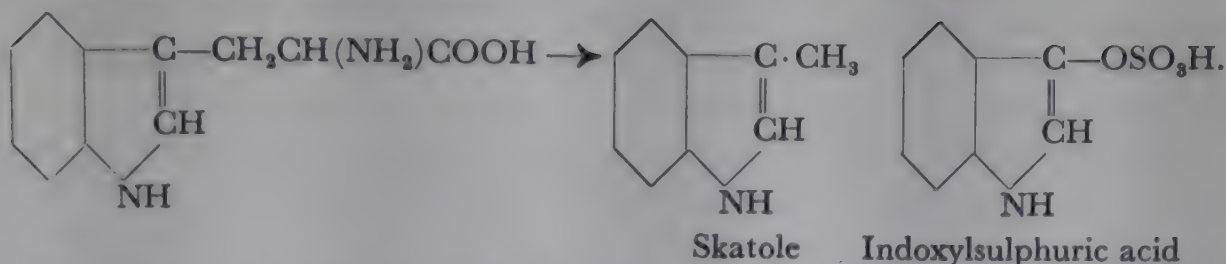
As far as the mechanism of the degradation of amino-acids to alcohols is concerned, it must be assumed that the process starts with a dehydrogenation of the amino-acid to an imino-acid. The latter then breaks down either according to scheme (a) into an aldimine, and then into an aldehyde, or according to scheme (b) into a ketonic acid and an aldehyde. The aldehyde is finally reduced to an alcohol:



The amino-acids can undergo different degradation reactions in the animal organism, tyrosine giving *phenol* and *p-cresol*, tryptophan giving *skatole* (a repulsive smelling constituent of fæces) or *indoxyl*, the latter occurring in the urine of herbivorous animals as *indoxylsulphuric acid*. The degradation is brought about by intestinal bacteria, which attack the amino-acids introduced with the food. In the case of tyrosine the reactions proceed through the following stages:



The degradation of tryptophan:

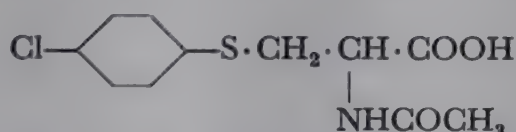


The organism makes use of different amino-acids under normal or special conditions to combine or "conjugate" them with other substances. Thus the urine of the horse always contains large quantities of *hippuric acid*, i.e. benzoylglycocoll, $\text{C}_6\text{H}_5\text{CO} \cdot \text{NHCH}_2\text{COOH}$, and this substance also occurs in human urine after ingestion of benzoic acid or substances which can be converted into benzoic acid.

Birds use ornithine in a similar way, coupling it with benzoic acid, and dibenzoyl- $\text{NHCH}_2\text{CH}_2\text{CH}_2\text{CHCOOH}$

ornithine, or *ornithuric acid*, $\begin{array}{c} | \\ \text{COC}_6\text{H}_5 \end{array} \begin{array}{c} | \\ \text{NHCOC}_6\text{H}_5 \end{array}$, is found in the

excrement. Dinicotyl-ornithine (nicotinic acid derivative of ornithine) is a metabolic product of the chicken. Phenylacetic acid is excreted by animals as *phenaceturic acid*, $\text{C}_6\text{H}_5\text{CH}_2\text{CONHCH}_2\text{COOH}$ (conjugated with glycocoll), and chlorobenzene is combined with cysteine and excreted as

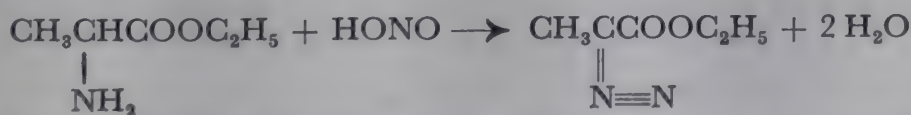


It appears justified to regard such conjugations of the amino-acids with alien substances as detoxication processes carried out by the body.

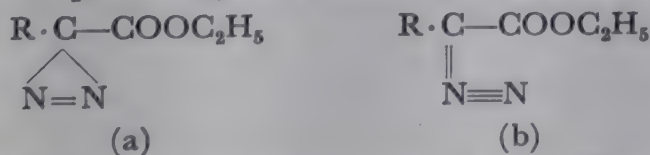
To the same class of compounds belong *glycocholic acid* (glycocoll-cholic acid conjugate) and *taurocholic acid* (taurine-cholic acid), which occur in bile.

Methionine is a biological methylating agent which, for instance, plays a part in the formation of choline and creatine *in vivo* (du Vigneaud).

An important class of derivatives of amino-acids was discovered by Curtius by the action of nitrous acid on the esters of α -amino-acids. They are thus converted into the esters of the *diazo-acids*, compounds which belong to the class of aliphatic diazo-compounds:



Two different views concerning the constitution of the **aliphatic diazo-compounds** exist, one preferring the formula (a) the other formula (b):



Weighty reasons can be given in support of both. The question cannot yet be regarded as solved. Possibly no unequivocal distinction can be drawn between the two, since two systems of this kind will presumably easily be converted one into the other.

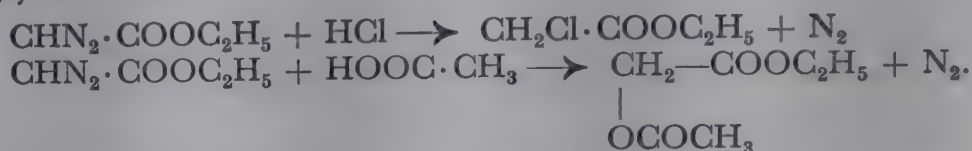
The *free* α -amino-acids do not give stable diazo-acids, although these are

probably also formed as intermediate products by the action of nitrous acid, breaking down, under the influence of water, immediately into hydroxy-acids and nitrogen. On the other hand, diazo-acid amides, $N_2:C(R)CONH_2$, and diazo-acid nitriles, $N_2:C(R) \cdot CN$, exist.

Diazo-acetic ester, $N_2:CH \cdot COOC_2H_5$, is a yellow oil, insoluble in water. When impure it quickly decomposes, but the pure substance can be distilled without decomposition. Its boiling point is 140° (720 mm). All aliphatic diazo-compounds are exceedingly reactive. By the action of water containing a trace of sulphuric acid diazo-acetic ester breaks down into glycolic ester and nitrogen:



Hydrochloric acid gives chloroacetic ester, and organic acids produce acyl derivatives of glycolic ester:

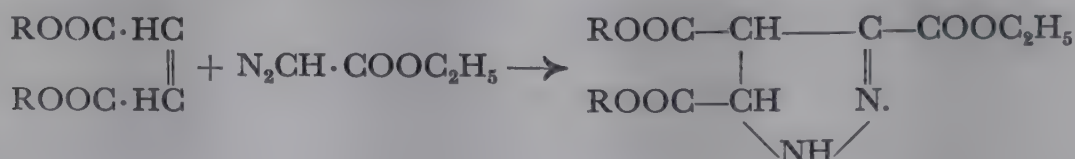


Since the velocity of the decomposition, and hence the rate of liberation of nitrogen, depends on the hydrogen ion concentration, the degree of dissociation, and with it the strength of an acid can be found by determining the volume of nitrogen, evolved in a given time (Bredig).

By controlled alkaline reduction (ferrous oxide) the aliphatic diazo-compounds can be reduced to hydrazones:



The strongly unsaturated nature of diazo-acetic esters is also made evident by the fact that they can polymerize under the influence of alkalis to heterocyclic compounds, (which will be considered in another part of this book), and by their capacity to add on to double bonds. For example, fumaric ester and diazoacetic ester combine to form a pyrazoline derivative:



The simplest aliphatic diazo-compound is DIAZOMETHANE, $CH_2 \begin{array}{c} \diagup N \\ || \\ \diagdown N \end{array}$ or

$CH_2 = N \equiv N$, a yellow gas, readily volatile with ether vapour. Its boiling point is about 0° . It is very poisonous. To prepare it nitrosomethylurethan is usually acted upon with alkali, alcoholic potash being added drop by drop to an ethereal solution and the mixture heated. The yellow diazomethane distils over with the ether (v. Pechmann):

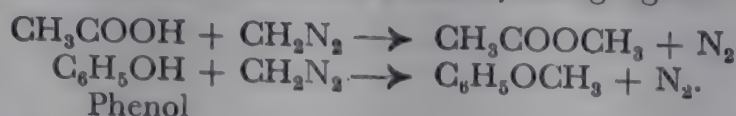


According to Staudinger the compound is also obtained by the action of chloroform and caustic soda on hydrazine:



Diazomethane readily converts acids quantitatively into their methyl

esters, phenols into their methyl ethers, and even unsaturated and polyhydric alcohols can be partially converted into ethers. The substance therefore has considerable preparative importance as a methylating agent:



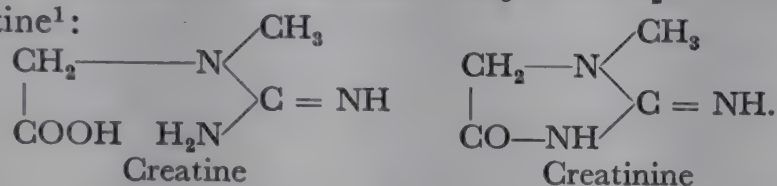
Under the influence of sunlight, diazomethane may even replace the hydrogen attached to a carbon atom C—H by methyl. When, for example, a solution of diazomethane in diethyl ether is exposed to light, ethyl *n*-propyl ether and ethyl isopropyl ether are formed (H. Meerwein):



As a rule it shows the same reactive nature as diazo-acetic esters, particularly being also inclined to add on to ethylenic and acetylenic derivatives, thus forming heterocyclic ring-systems.

GLYCOCOLL, GLYCINE, AMINOACETIC ACID. The simplest α -amino-acid, glycoll, glycine, or aminoacetic acid, must be briefly mentioned as it is the starting point for various important natural products.

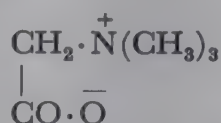
Its N-methyl derivative is *sarcosine*, $\text{CH}_3\text{NH}\cdot\text{CH}_2\text{COOH}$, a degradation product of creatine¹:



A creatine-phosphoric acid, $\text{HOOC}\cdot\text{CH}_2\text{N}(\text{CH}_3)\text{C}(:\text{NH})\cdot\text{NHPO}_3\text{H}_2$, phosphagen, occurs in the muscle of vertebrates. It breaks down on contraction of the muscle, and is re-synthesized on relaxation. The muscle of invertebrates contains arginine-phosphoric acid in place of creatine-phosphoric acid, its function being similar.

Creatinine is excreted by human beings and many other mammals normally through the urine. It often occurs in plants. It is more soluble in water than creatine.

Betaine, completely methylated glycine,

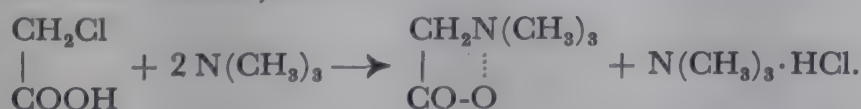


occurs very widely in nature. It is found in an extraordinarily large number of plants, usually together with *choline*, the corresponding alcohol,



Its occurrence in considerable quantities in beet-sugar molasses is made use of, as already mentioned, for the preparation of trimethylamine (see p. 133). Betaine is also wide-spread in the animal kingdom. It is an important methyl donor, i.e. biological methylating agent (e.g. in the formation of choline and creatine).

Betaine can be prepared artificially by the methylation of glycine, or from chloracetic acid and trimethylamine:



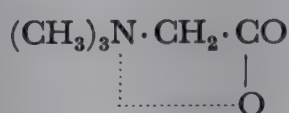
¹ A. HUNTER, *Creatine and Creatinine*, London, (1928). — H. H. BEARD, *Creatin and Creatinin Metabolism*, New York, (1944).

The compound is exceedingly soluble in water, reacts neutral, and melts (anhydrous) at about 293° .

A. Girard has introduced the use of the hydrazide of betaine, $\text{Cl}(\text{CH}_3)_3\text{NCH}_2\cdot\text{CONHNH}_2$, as a reagent for ketones, with which it forms *water-soluble* hydrazone derivatives which can be readily separated from impurities insoluble in water ("Girard's reagent").

Whilst at first the name "betaine" was only used to designate the above-mentioned substance, in later times the term has been extended to include in general the N-trialkyl derivatives of amino-acids. It has been found that substances of the betaine type are fairly widely spread in the animal and vegetable kingdoms, the compounds occurring in this way being frequently just those whose structures are derived from those of the natural amino-acids, so that a genetic connection between the two classes of compounds may be assumed.

Later the term "betaine" has taken on a still more general meaning. The term means to-day internal (intramolecular) salts of quaternary ammonium, oxonium, sulphonium, etc., bases in general. Substances with this betaine structure will therefore be met with in many later chapters, particularly in connection with certain classes of organic dyestuffs. Every betaine is a "zwitter-ion", it has a polar character. In its molecule a positive and a negative ion are combined. Instead of using formula (a) the structure of a betaine may thus also be expressed by formula (b) which shows the ionic properties of its groups of atoms (P. Pfeiffer):

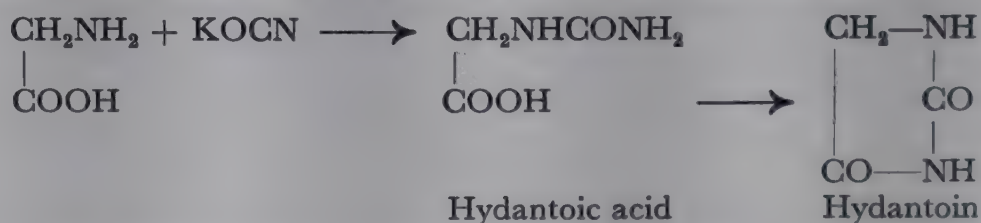


(a)



(b)

Hydantoin is to be considered as a derivative of glycine. It is best prepared by condensing glycine with potassium cyanate to form hydantoic acid, and eliminating water from the latter by boiling with hydrochloric acid:



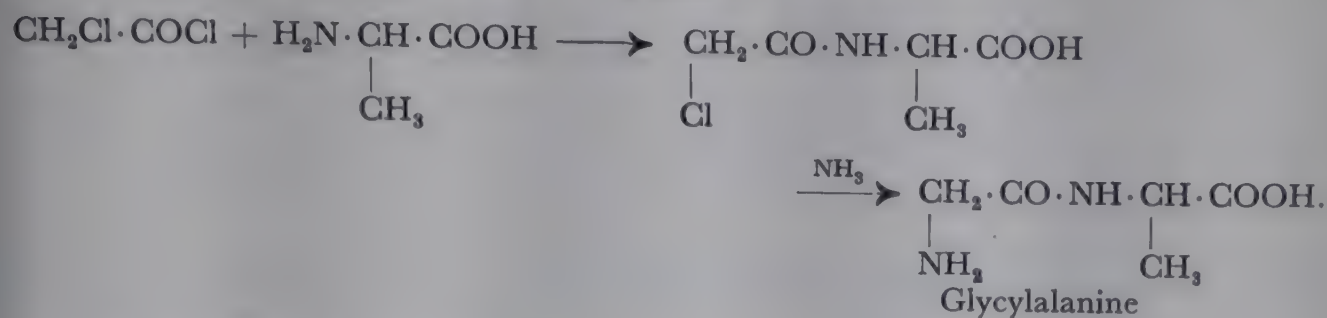
Hydantoin has been found in molasses. C-homologues (phenylethylhydantoin = nirvanol) are used as hypnotics.

Polypeptides. Under this heading are comprised amide-like amino-acid derivatives formed by the amino-group of an amino-acid molecule combining with the carboxyl of another molecule with elimination of water. The amido-linking is, however, not confined to two amino-acid molecules. Any number of such molecules can link up in the same way:

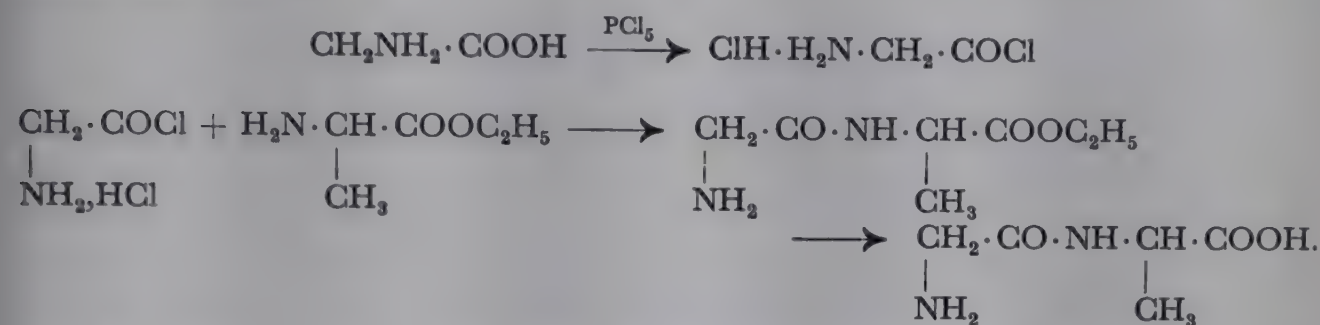


Moreover, the single constituents need not all be of the same kind. All amino-acids can be members of the chain, and need not be in any particular sequence. There is thus an almost inexhaustible number of possible variations. The number of possible combinations can easily be calculated by permuting the number of available amino-acids. The calculation shows that even from ten different amino-acids, over 3,600,000 different polypeptides could be built up.

The synthesis and investigation of these compounds has been largely the work of E. Fischer. They may be prepared by combining the α -halogen-substituted carboxylic acid chlorides with amino-acids, and then exchanging the halogen of the product for an amino-group by treating it with ammonia:

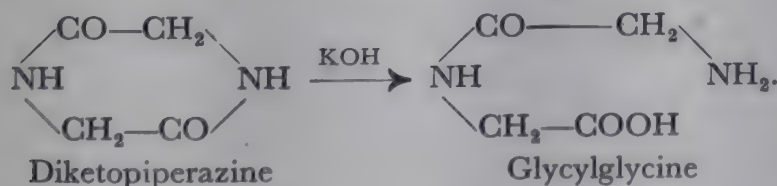


On the other hand, it is also possible to convert the amino-acids first into the hydrochloride of the amino-acid chloride, and then to combine this with an amino-acid ester:



In more recent years a synthesis of polypeptides due to M. Bergmann has assumed considerable importance. It depends on the preliminary introduction of the carbobenzyloxy ("carbobenzoy") group into the amino-group of an amino-acid by means of carbobenzyloxy chloride, $\text{C}_6\text{H}_5\text{CH}_2\text{OCOCl}$. The free carboxyl group of the thus acylated amino-acid is then chlorinated and the acid chloride produced is made to react with a second molecule of amino-acid. Finally, the carbobenzyloxy radical in the dipeptide formed is removed by *reduction*. The advantage of this method over the older polypeptide syntheses is that the removal of the acyl radical (carbobenzoy radical) introduced to protect the amino-group can be accomplished by *reduction*, and need not be done by hydrolysis, so that any subsequent fission of the peptide linkage is avoided.

In addition to these quite general syntheses, there are some other methods of making polypeptides which are of only limited application. Dipeptides, for example, can often be made by rupturing the ring of diketopiperazines, which can be regarded as internal amides of the amino-acids:



The importance of the polypeptides is based on the fact that they possess various properties in common with the native proteins. Aqueous solutions of higher members of this group froth like those of proteins, and show, like the latter, the biuret reaction (violet coloration with an alkaline solution of copper sulphate).

They can be salted out by neutral salts in the same way as proteins. Their behaviour towards erepsin is particularly important. Many polypeptides are hydrolysed by this enzyme, which occurs in the mucosa of the small intestine. This similarity in the behaviour of proteins and polypeptides, and also the fact that by careful hydrolysis of proteins dipeptides are often, and even tripeptides occasionally obtained, led E. Fischer to assume that proteins are built up like a polypeptide chain, and consist of a mixture of numerous compounds of this kind with high molecular weights. He therefore endeavoured to prepare high-molecular members by synthesis and succeeded in obtaining a polypeptide which contained 18 amino-acid constituents:



L-Leucyltriglycyl-L-leucyltriglycyl-L-leucyloctaglycylleucine.

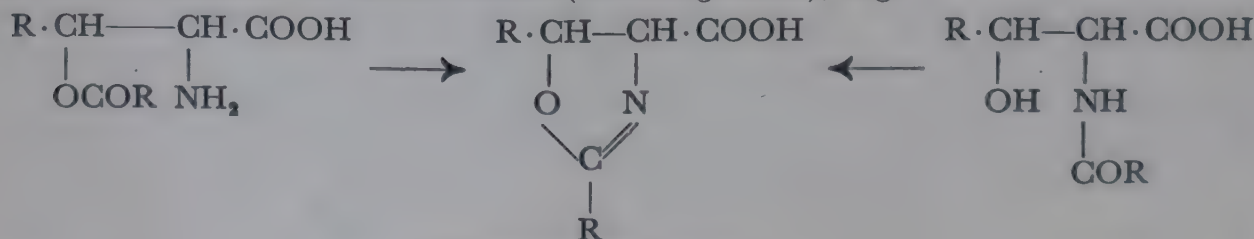
E. Abderhalden later obtained an analogous compound made up of 19 amino-acids.

However, the proteins show many properties which are not observed with polypeptides. Thus, many proteins are broken down by the enzyme pepsin to a number of rather complex constituents, but polypeptides undergo decomposition by pepsin only rarely. The polypeptides are often more stable towards chemical reagents than native proteins. Hence the view now prevails that other kind of linkages must also be present in proteins in addition to the polypeptide linkings. There might be *ester-like groups* (Kossel), in which, for example, serine takes part with its hydroxyl group; *diketopiperazine derivatives* (Abderhalden) might be present, possibly in the *enolic form*:



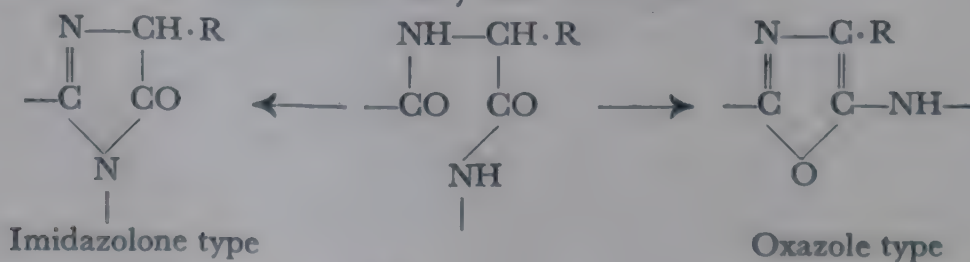
Diketopiperazine derivative Enolic diketopiperazine derivative

Also, *oxazoline* groups have been assumed to be present in proteins, formed by the anhydridization of amino-acids (M. Bergmann), e.g.:



"Oxazoline peptide"

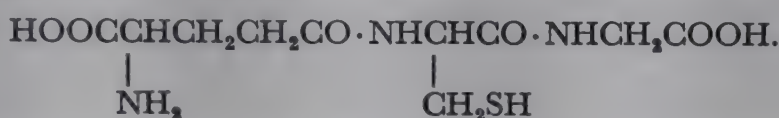
Imidazolone and *oxazole* structures may also occur:



At present, however, all these assumptions have not yet been satisfactorily confirmed experimentally, since only diketopiperazine derivatives have been isolated, apart from polypeptides, by the hydrolysis of proteins, and opinion on the matter is divided between the formation of these compounds by a simple decomposition of proteins, or by a secondary reaction.

The experimental material available at present, however, agrees with the main point that proteins are largely built up on the principle of the polypeptide chain, the linking of the individual amino-acids taking place through the carboxyl group and the amino- and imino-groups (proline, hydroxyproline) in the α -position. The unsubstituted amino-acid radicals, or these radicals substituted by basic or acidic groups, project from the polypeptide chain, and may enter into secondary reactions with each other, or with the solvent. In these cases intramolecular condensations or reactions may be brought about with the aid of subsidiary valencies. Views supported by sufficient experimental evidence have so far not been put forward regarding the specially reactive groups of the protein molecules.

A tripeptide, GLUTATHIONE, is worth special mention. It is built up of glutamic acid, cysteine, and glycine, and has the composition $C_{10}H_{17}N_3SO_6$. The molecule thus consists of one each of these three amino-acids. The sequence in which the three acids are placed is known by synthesis of the tripeptide; it is a glutamyl-cysteinyl-glycerine of the formula:



Glutathione occurs in most cells (Hopkins) where it plays the part of an oxygen carrier. Being a mercaptan it is easily oxidized to the corresponding disulphide, and the latter is readily reduced again to glutathione. It also acts as an activator of the catheptic enzymes, i.e. the proteinases of the mucous membranes of the stomach, and other enzymes, which function in slightly acid media.

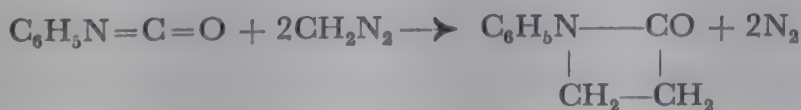
Glutathione is laevorotatory, the specific rotation being greatly dependent upon temperature.

The dipeptides CARNOSINE and ANSERINE have been isolated from meat extract and muscle. They are specially remarkable because they contain a β -amino-acid, β -aminopropionic acid, as a component. Carnosine is N-(β -aminopropionyl)-histidine, and anserine is its N-methyl derivative [N-(β -aminopropionyl)-1-methyl-histidine].

γ - and δ -amino-acids, etc., have been prepared synthetically. Up to the present they have not been met with in nature. Just as the γ -hydroxycarboxylic acids tend to form lactones (p. 263-4), γ - and δ -amino-acids easily split off water intramolecularly and give internal amides, or *lactams*:

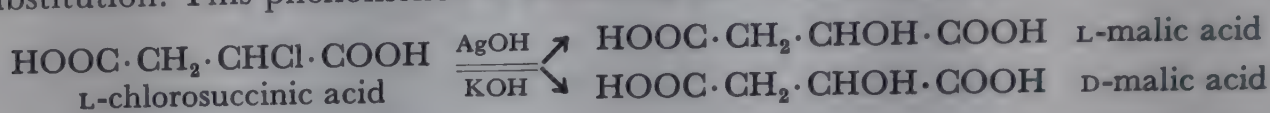


β -Lactams are little investigated and can only be obtained indirectly, as for instance, the β -lactam of N-phenyl- β -aminopropionic acid from phenyl isocyanate and diazomethane:

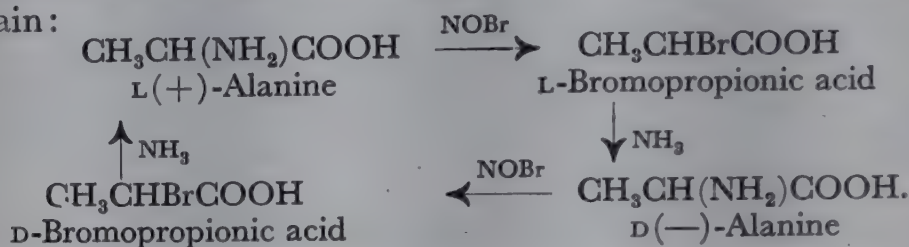


Stereochemistry of the α -amino-acids. All α -amino-acids with the exception of glycine contain asymmetric carbon atoms. Several interesting questions are connected with their optical activity.

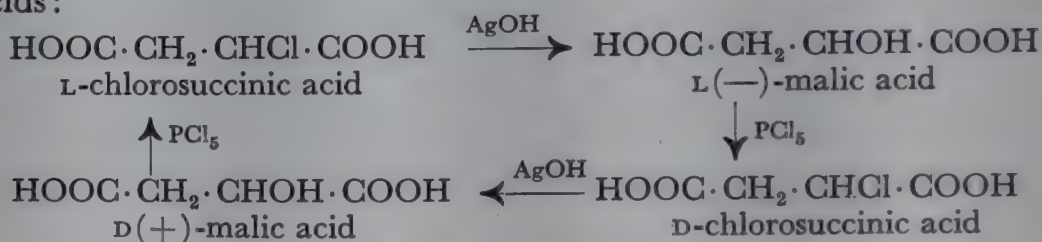
P. Walden first observed that by exchanging the chlorine atom in L-chlorosuccinic acid for a hydroxyl group, levorotatory, or dextrorotatory malic acid could be produced, according to the reagent used for removing the chlorine. Silver oxide gave L(—)-malic acid, caustic potash gave D(+)-malic acid. In one of these cases a change of configuration must therefore have occurred with the substitution. This phenomenon is known as the *Walden Inversion*:



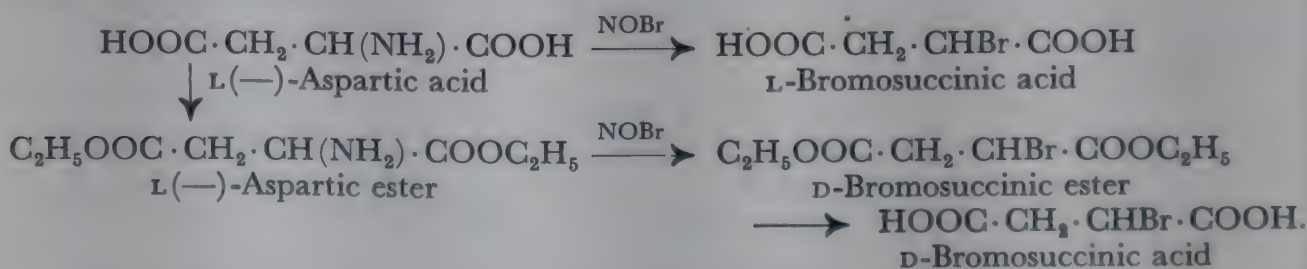
In amino-acid transformations numerous inversions of configuration have been observed. Thus, for example, L(+)-alanine can be converted by nitrosyl bromide into L-bromopropionic acid, which by the action of ammonia is converted into D(—)-alanine; by the action of nitrosyl bromide on the latter D-bromopropionic acid is formed, and from this, by the action of ammonia, L(+)-alanine is obtained again:



A similar cycle may be carried out with the active chlorosuccinic acids and malic acids:



The complicated relationships which are connected with the Walden inversion are also shown by the following observation: L(—)-aspartic acid is converted by nitrosyl bromide into L-bromosuccinic acid. If, however, L(—)-aspartic ester is prepared first and treated with nitrosyl bromide, the ester of D-bromosuccinic acid results:

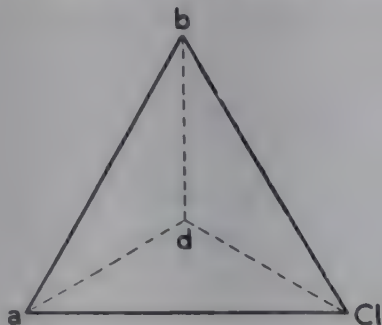


It is clear that changes in configuration often occur when substitution takes place at an asymmetric carbon atom, i.e. the incoming substituent does not take the place left vacant by the outgoing group, but some other place. When this is going to happen cannot be foretold. The nature of the other substituents, and of the reagent, and the reaction rate influence the course of the reaction. It appears highly probable that such inversions of configuration are not limited to

substitution reactions taking place at asymmetric carbon atoms. They probably occur also with symmetrical molecules quite generally, but the means are lacking to detect them.

To explain the phenomenon of the Walden inversion the following treatment due to A. Werner and P. Pfeiffer may be given: Suppose the four substituents at an asymmetric carbon atom are a, b, d, and Cl, arranged at the apices of a tetrahedron. There will be four fields of affinity present, limited by the following groups:

a b d
a b Cl
a Cl d
Cl b d



Suppose ammonia acts upon this compound. It is first attracted to one of these four fields of affinity. If this is one in which chlorine takes part, the ammonia radical enters in place of the chlorine. If, however, the ammonia finds itself at the particular moment when it comes into contact with the molecule, in the a, b, d affinity

field, one of these substituents jumps into the place vacated by the chlorine, and the amino-group takes another place. Thus a change of configuration, or "Walden inversion", has occurred.

It is clear that under these circumstances the *nature* of the substituents must determine the course of the substitution, since on them depends the nature of the fields of affinity.

In more recent times attempts have been made to make these views somewhat more precise. According to E. Bergmann a negative ion Y' approaches a polar molecule $R_1R_2R_3C-X$ at the positive end, i.e. towards the C atom, and reacts with it with expulsion of the negative ion X' :



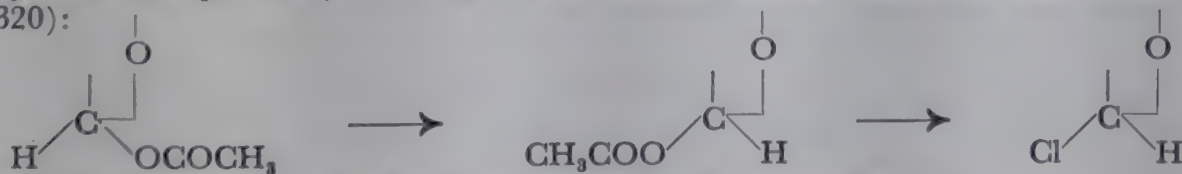
The new substituent Y thus does not enter the same place in the tetrahedron which has been vacated by X, and the Walden inversion has hence occurred. On the other hand, when reaction occurs with a positive ion, the latter approaches the negative side of the polar linkage, i.e. the X end, and combines with it to form a neutral molecule, whilst the remainder of the molecule becomes a positive carbonium radical:



The latter is stabilized in some way or other by entering into secondary reactions, whereby partial or complete racemization may occur, but never a Walden inversion.

According to this view the Walden inversion would chiefly be expected to occur if a negative ion of a polar, asymmetric, organic molecule is substituted by another negative ion.

It appears that in certain substitution processes which are accompanied by a Walden inversion, the reagent used in the reaction first causes inversion, whereupon normal substitution follows. Thus E. Pacsu found that when stannic chloride acts upon β -acetylglucose in chloroform, α -acetylglucose is first formed, whereupon, after long heating, CH_3COO- is replaced by chlorine, and acetochloroglucose is formed (for this reaction see p. 320):

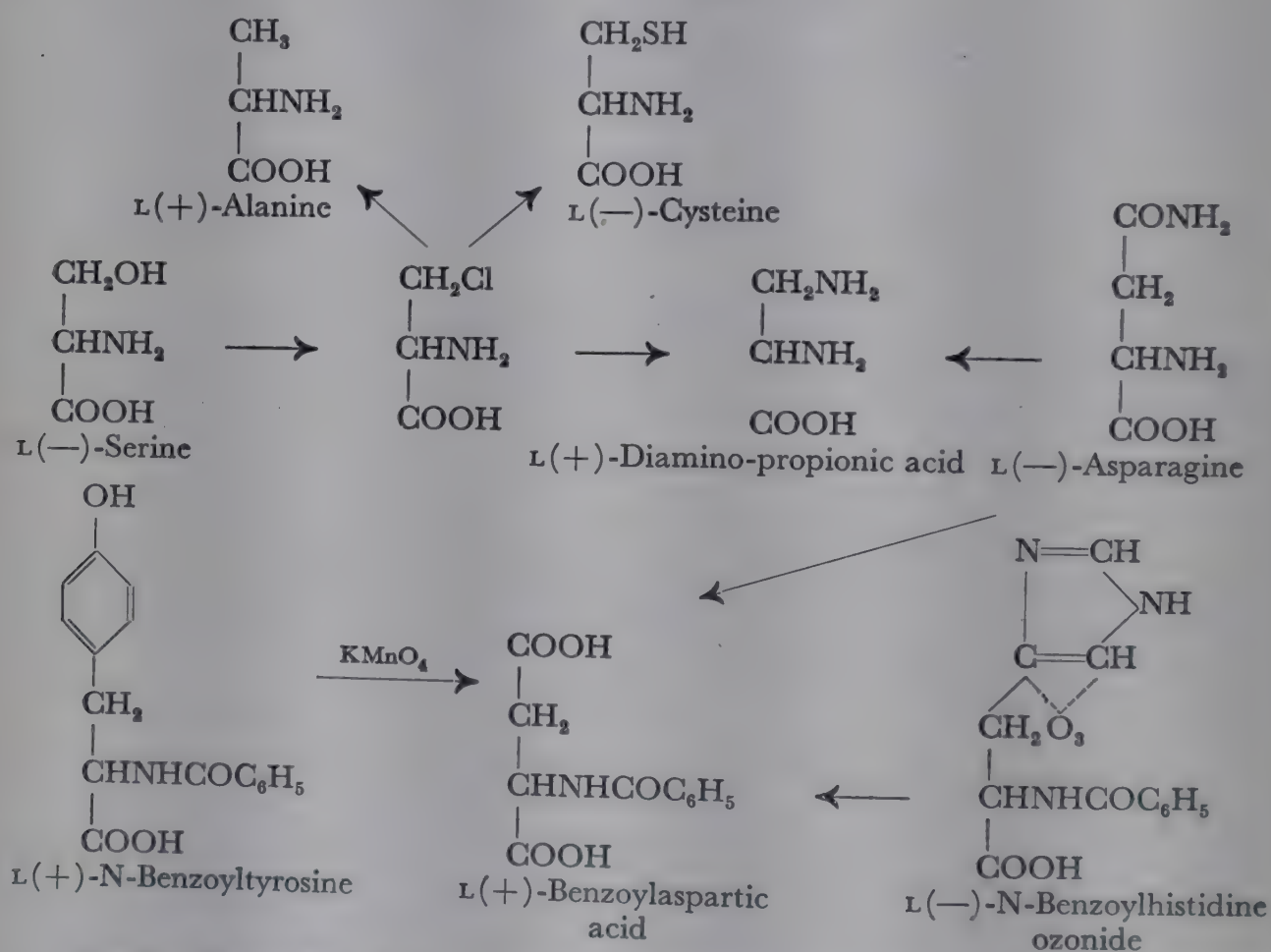


β -Glucosides are converted into α -glucosides in a similar fashion.

The knowledge of the Walden inversion thus gained, makes it clear that to discover whether two compounds have similar or different configurations it is

indispensable to convert one compound into the other *without any substitutional changes* at an asymmetric carbon atom. Only when this is the case is it possible to say with certainty that an unequivocal picture of their configurative relationship has been obtained. This has sometimes been possible for a number of α -amino-acids.

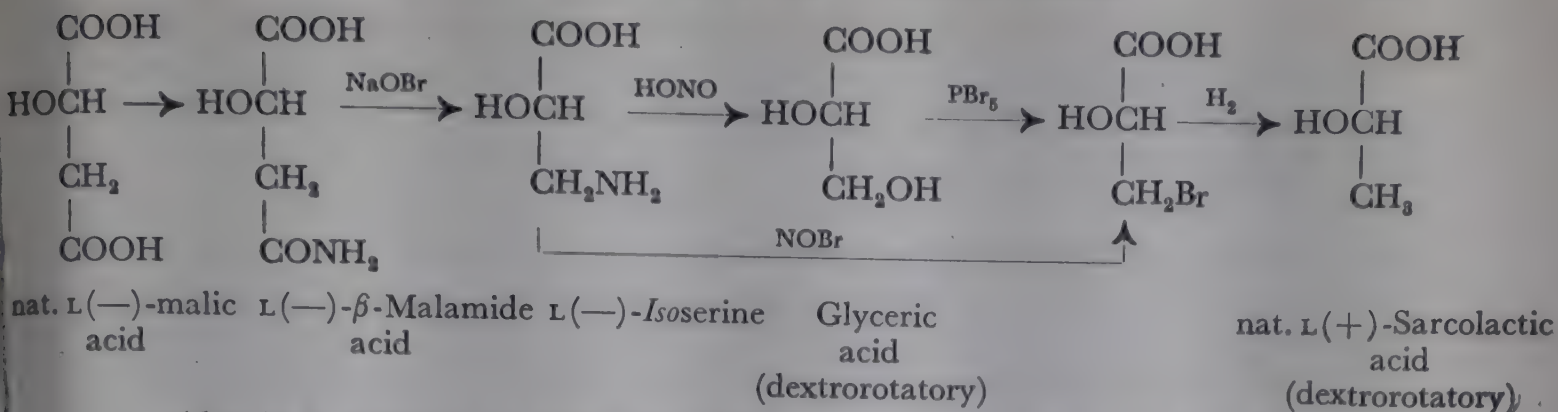
Starting with natural¹ L(—)-serine, by acting upon it with phosphorus pentachloride, α -amino- β -chloropropionic acid can be obtained; with sodium amalgam the latter gives natural L(+)-alanine, and with barium hydrosulphide, Ba(SH)₂, natural L(—)-cysteine. By the action of ammonia it is converted into into L(+)- α,β -diaminopropionic acid, which can also be obtained from natural L(—)-asparagine by Hofmann's degradation. The oxidation by means of ozone of L(—)-N-benzoylhistidine on the one hand, and the oxidation with KMnO₄ of L(+)-N-benzoyltyrosine obtained from natural L(—)-tyrosine on the other, gives the N-benzoyl derivative of natural L(—)-aspartic acid:



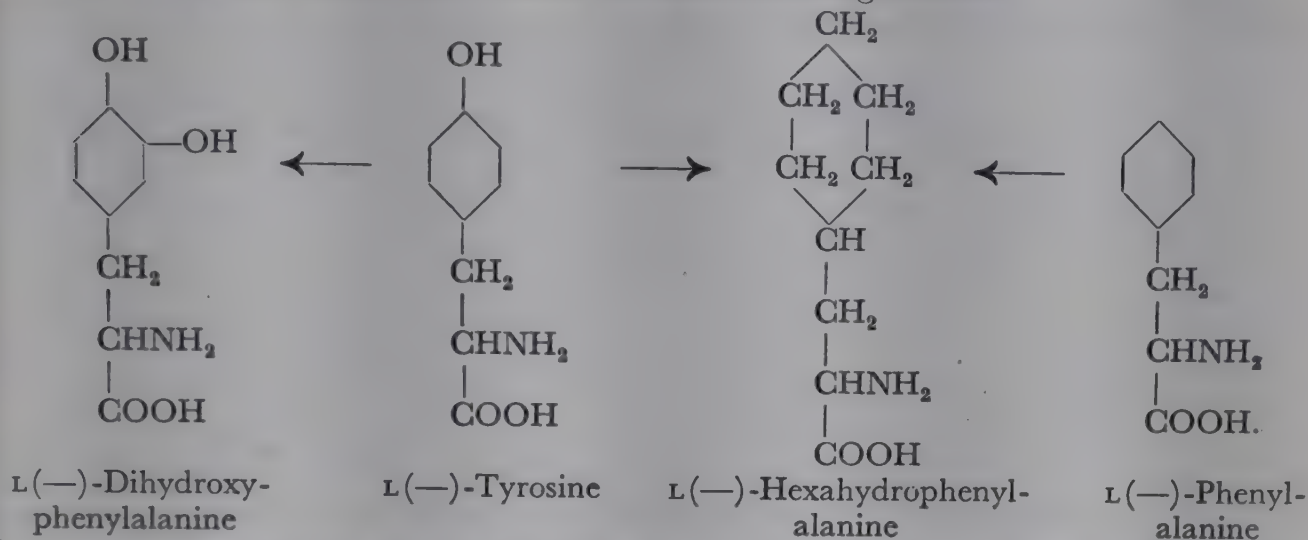
Finally, it may be shown that L(—)-leucine, natural norvaline, norleucine, ornithine, lysine, proline, methionine, threonine, and natural glutamic acid also correspond configuratively to L(—)-aspartic acid, so that all natural amino-acids, so far as their configurations have been elucidated, are built up according to the same "L"-configuration.

The same stereochemical structure occurs in a series of naturally occurring α -hydroxy-acids, namely natural L(—)-malic acid, dextrorotatory glyceric acid, and dextrorotatory sarcolactic acid, which are connected by the following series of reactions:

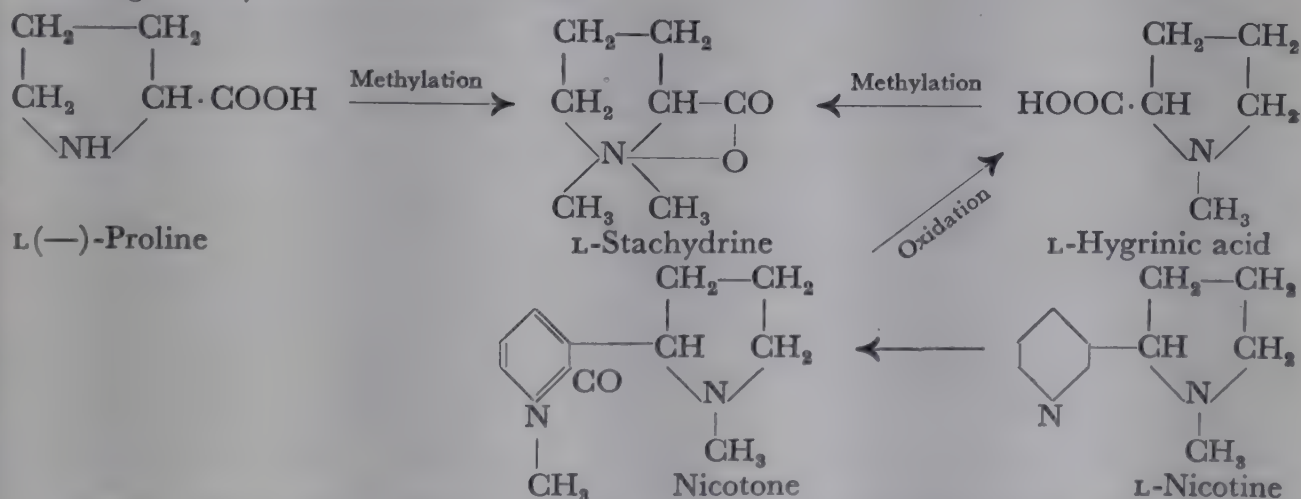
¹ By "natural" amino-acids are meant here those that are exclusively or almost exclusively found in the proteins. See also page 307.



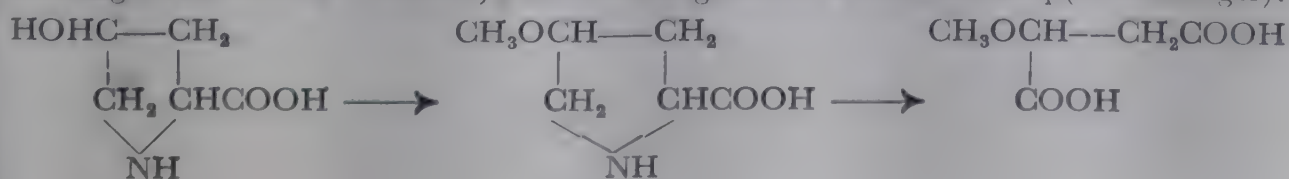
Also it is possible to convert natural L(-)-tyrosine on the one hand into L(-)-dihydroxyphenylalanine, and on the other hand to reduce it to L(-)-hexahydrophenylalanine. The latter can also be obtained from phenylalanine. Hence these three amino-acids also possess the same L-configuration:



The most diverse natural products with an asymmetric carbon atom in general appear to have analogous spatial structures. For example, the protein amino-acid proline, and the alkaloids L-stachydrine (see Ch. 65) and L-nicotine (see Ch. 65) have analogous configurations since all these compounds can be converted into L-stachydrine without attacking the asymmetric carbon atom:



The spatial position of the hydroxyl group in natural hydroxyproline has also been ascertained, as it has been possible to convert natural L(-)-hydroxyproline through the O-methyl ether into D(+)-methoxysuccinic acid. L(-)-Hydroxyproline therefore has a L-configuration at the C-atom 2, and a D-configuration at the C-atom 4 (A. Neuberger):



D-Amino-acids are but seldom found in nature. D-Glutamic acid occurs in the immunologically specific capsular substance of the *Anthrax bacilli* (V. Brückner); D(+)-proline has been obtained by Jacobs by hydrolysis of ergotinine. Penicillin (q.v.) also is derived from a D-amino-acid.

Since the configurations of the most important α -hydroxy-acids, α -amino-acids, and α -halogen-substituted acids (see p. 253) have now been arrived at, it is possible by considering several substitution reactions to say which reagents exert an inverting effect in these reactions. These result are given schematically in the following table, in which the straight arrow represents a substitution without Walden inversion, and the curled arrow represents one with inversion.

In this lactic acid-malic acid group a certain reagent always reacts in the same way, inverting or non-inverting. Other groups of substances, on the other hand, show deviations from this scheme (K. Freudenberg):

	Lactic acid Malic acid	Chloro-, Bromo-, propionic acid, Chloro-, Bromo-, succinic acid	Alanine Aspartic acid	Alanine ester Aspartic ester
Ag ₂ O	←	←		
NOOH	←	←	←	
NOCl		←	←	○
NOBr		←	←	○
PCl ₅ , SOCl ₂	○ →			
PBr ₅		○ →	○ →	
NH ₃	← ○			
KOH	← ○			

II. Proteins¹

Native proteins fall into two groups:

1. SIMPLE PROTEINS. These give amino-acids only on hydrolysis. Albumins, globulins, gliadins, histones, protamines, glutelins, and the scleroproteins (keratin, elastin, gluten, collagen, etc.) belong to this group.

2. CONJUGATED PROTEINS OR PROTEIDS. In addition to the protein complex, these compounds contain a component of a totally different nature, the phosphoproteins (casein²) contain a phosphorus group, the glucoproteins (ovalbumin, mucin) contain carbohydrates, the nucleoproteins contain nucleic acids.

COMPOSITION AND STRUCTURE. The analytical composition of most proteins varies only within narrow limits. The proteins contain approximately 50–55 % carbon, 6.5–7.3 % hydrogen, 15–18 % nitrogen, 21–24 % oxygen, 0–2.4 % sulphur, and there is always ash. The type and number of individual constituents of which they are made up are, however, very different. About 25 amino-acids have so

¹ See WOLFGANG PAULI, *Colloid Chemistry of Proteins*, Philadelphia, (1922). — S. P. L. SØRENSEN, *Proteins*, New York, (1925). — ALBRECHT KOSSEL, *Protamine und Histone*, ed. by Segfr. Edlbacher, Vienna, (1929). — THE SVEDBERG, *Les molécules protéiques*. Actualités scientifiques et industrielles Nr. 783, Paris. — DOROTHY LLOYD, AGNES SHORE, *Chemistry of the proteins*, 2nd. ed., London, (1939). — E. J. COHN, J. T. EDSALL, *Proteins, Amino Acids and Peptides*, New York, (1943). — M. L. ANSON and JOHN T. EDSALL, *Advances in Protein Chemistry*. Vol. 1 and 2, New York, (1944/45).

² E. SUTERMEISTER and F. L. BROWNE, *Casein and its Industrial Applications*, 2nd ed., London, (1939).

far been detected in the products of hydrolysis of proteins. It is possible that some, occurring in native proteins, are still unknown, as their isolation presents great difficulties. In the hydrolysis, ammonia is always eliminated, having been formed from the acid amides occurring in the proteins (asparagine, glutamine) and perhaps from ureido-acids present.

There is an extraordinarily large number of different kinds of proteins. Not only does the nature and amount of the amino-acids vary from protein to protein, but the proteins themselves show great differences in their physical properties. Some of them, such as the albumins, form colloidal solutions with water, others, such as the globulins are insoluble in water, but dissolve in solutions of neutral salts (e.g. sodium chloride). Keratin, elastin and fibroin and similar proteins are completely insoluble. When colloidal solutions of proteins are formed there are further differences in the ease with which they can be salted out or precipitated. Use is made of these differences in solubility for the separation of proteins. It follows, however, from the method on which they are based, that these separations can never be complete. No protein isolated can even now be said with certainty to be pure. Reliable methods for detecting the purity of the proteins are wanting. It is possible to obtain many proteins in a crystalline form, for example the albumin of serum and egg, but even now it cannot be said exactly what these crystals are. For the growth of the crystals, the presence of certain inorganic salts, e.g. ammonium sulphate (Sørensen) is necessary.

Just as uncertain are the molecular weights of the proteins. From the iron content of ox-hæmoglobin it has been concluded that its molecular weight is between 16,000 and 17,000, and from the content of loosely bound sulphur in casein, the molecular weight of the latter is found to be 16,000, etc. These conclusions, however, are only justified if these proteins can be regarded as homogeneous and if the characteristic atoms only occur once in the molecule. Cryoscopic determinations of molecular weights are not very easily carried out since the soluble proteins only form colloidal solutions. The observed depressions of the freezing point are small, and the values for the micellar weights correspondingly high. More suitable methods are based on the rate of diffusion and on the viscosity. Furthermore, a method due to Svedberg of determining the size of the particles on the basis of their sedimentation velocity, using the ultra-centrifuge, is of practical use.

The molecular weights, determined by means of the ultra-centrifuge, differ considerably from protein to protein, e.g. serum albumin 70,000, lactalbumin 17,400, lactoglobulin 41,800, egg albumin 44,000, serum globulin 167,000, legumin 208,000, casein 75,000–375,000, hæmocyanin (from *Octopus vulgaris*) 2,000,000. How far these figures are actual molecular weights, or how far they are micellar weights, is difficult to say.

On the other hand, the ultra-centrifuge method makes it possible to test the homogeneity of a protein preparation with respect to its particle size, on the basis of the different sedimentation velocities.

Colloidal solutions of proteins may be precipitated or coagulated by a series of reagents. The precipitation may be reversible or irreversible, i.e. the precipitate retains its solubility, or it becomes insoluble. Irreversible coagulation occurs if the protein solution is boiled, particularly after addition of some acetic acid and sodium chloride, or other electrolytes. This reaction is commonly used for the

detection of dissolved proteins (e.g. their detection in urine). Mineral acids (nitric acid, chloroplatinic acid, phosphotungstic acid, phosphomolybdic acid, metaphosphoric acid, ferrocyanic acid), picric acid, tannic acid, and heavy-metal salts bring about irreversible precipitation. Proteins can be precipitated from their aqueous solutions by the addition of alcohol or acetone; they then retain their solubility. They can also be reversibly precipitated by different neutral salts, such as ammonium sulphate, sodium sulphate, and magnesium sulphate. For this purpose, however, a definite salt concentration is needed the lower limit of which varies from protein to protein (cf. albumins and globulins).

In contrast to this, sodium chloride can dissolve certain proteins, e.g. the globulins.

Many colour reactions are available for the detection of small amounts of proteins. They frequently depend, however, on the presence of certain amino-acids in the protein:

- | | |
|--|---|
| (a) The biuret reaction. | This reaction is given by all proteins, and indicates the presence of peptide linkages. Method of carrying out the test: add much sodium hydroxide and a little copper sulphate. Violet coloration. |
| (b) Xanthoproteic reaction. | Treatment with strong nitric acid gives a yellow coloration (nitration), which becomes orange on addition of ammonia. The reaction indicates the presence of phenylalanine, tyrosine, and tryptophan. |
| (c) Millon's reaction. | By heating the protein solution with a solution of mercury in nitric acid containing nitrous acid, a red-brown precipitate is formed (test for tyrosine). |
| (d) Pauly's reaction. | Diazobenzenesulphonic acid (see p. 466) gives a red coloration when added to a protein solution made alkaline with sodium carbonate. The colour changes to yellow-red on acidification (test for tyrosine and histidine). |
| (e) Reaction of Adamkiewicz, Hopkins and Cole. | On adding glyoxylic acid and concentrated sulphuric acid to a solution of a protein a blue-violet coloration is produced (test for tryptophan). |
| (f) Ninhydrin test. | Amino-acids, polypeptides, and peptones give a blue coloration on boiling with an aqueous solution of triketohydrindene hydrate (ninhydrin). |

With regard to the hydrolysis of proteins it has already been said that acid hydrolysis with strong hydrochloric or sulphuric acids is usually employed, and less often alkaline hydrolysis. Both give amino-acids. The enzymatic digestion of proteins is a very effective method of bringing about hydrolysis. The enzymes which act on proteins in the animal organism may be classified into three groups:

(a) Peptic enzymes, *pepsin* (in the stomach). These are most effective in weakly acid solution (N/10 hydrochloric acid). The process breaks down native proteins chiefly to the peptide stage. Recently it has been found, however, that several simple polypeptides are also hydrolysed by pepsin.

(b) Tryptic enzymes, *trypsin* (in the pancreas). These exert their greatest effect in a very weakly alkaline medium, and hydrolyse native proteins and the products of pepsin hydrolysis, and higher peptides. The pancreas contains various enzymes which take part in the hydrolysis of proteins, and act in weakly alkaline or neutral media, e.g. pancreas pepsin, carboxypolypeptidase, aminopolypeptidase, and dipeptidases. The dipeptidases and aminopolypeptidases are only effective if the substrate contains free amino-groups. They therefore enter into combination with the latter, probably by means of aldehyde or keto groups (production of Schiff bases). The carboxypolypeptidase reacts only with polypeptides which contain free carboxyl groups, and even then only if the amino-acids which contain the free carboxyl groups are of a certain kind, e.g. tyrosine or tryptophan, or if the free amino-groups of the polypeptide are acylated (e.g. benzoylated). The NH-groups also participate in attaching the dipeptidase.

(c) Ereptic enzymes (from the mucous membranes of the small intestine), *erepsin*. These act on polypeptides but not on native proteins. Amongst the ereptic enzymes there is an aminopolypeptidase and a dipeptidase. The former hydrolyses only polypeptides with free amino-groups, e.g. tetraglycinamide. It seems, therefore that it adds on to free amino-groups (H. v. Euler and K. Josephson, Waldschmidt-Leitz).

Of course, plants also contain protein-hydrolysing enzymes (e.g. papain, etc.)

The first products of the hydrolysis of proteins are called albumoses. These cannot be coagulated, but can be salted out like proteins. At the next stage in the degradation we have substances which can neither be coagulated nor salted out. They are called peptones. The albumoses and peptones consist probably, for the main part, of compounds of polypeptide nature. Our knowledge of these important intermediate stages of protein hydrolysis is, however, still rather imperfect.

Types of proteins. (1) **ALBUMINS.** Albumins are neutral substances, which are soluble in water, and can be precipitated by neutral salts if the solution is 70–100 % saturated with salt. They usually contain a large percentage of sulphur, but no glycine. To the albumins belong, amongst others, serum albumin, lactalbumin, ricin (from castor-oil seeds), leucosin (from various kinds of grain), legumelin (from peas and vetches).

(2) **GLOBULINS.** They are insoluble in water but dissolve in dilute solutions of neutral salts, dilute acids and alkalis. Half-saturation with ammonium sulphate salts them out. To the globulins belong, e.g. serum globulin, ovoglobulin, lactoglobulin, fibrinogen of blood, myosin and myogen from muscle, edestin from hemp, phaseolin from a species of bean, and the globulins of grain.

(3) **GLIADINS** (or prolamins). These proteins are distinguished from all others by their solubility in 70–80 per cent alcohol. They are rich in proline and glutamic acid. To this class belong the gliadin of wheat, zein of maize, and hordein of barley.

(4) **GLUTELINS.** These are similar to globulins in many ways, but are only soluble in dilute alkalis and acids, and not in solutions of neutral salts. Glutenin from wheat and maize, and oryzenin from rice belong to this class.

(5) **HISTONES** are readily soluble in water giving a solution with a strong alkaline reaction, and can be precipitated again by adding small quantities of salt or by ammonia. Their basic character is due to the high percentage of diamino-acids which they contain (up to 30 per cent). They are digested by all proteolytic enzymes. Occurrence: in blood corpuscles, leucocytes, and in the spermatozoa of fish.

(6) **PROTAMINES.** These consist almost entirely of diamino-acids, especially arginine, which occurs up to the extent of 87 per cent. They therefore react strongly basic and form salts with acids. Their molecular weight is relatively very low (Kossel). They are readily soluble in water, and the solutions are not coagulated on heating. Protamines occur in fish, e.g. salmin in the salmon, and clupein in the herring.

Waldschmidt-Leitz assumes *clupein* to contain the ratios 10 mols. arginine: 1 mol. proline: 1 mol. alanine: 2 mols. serine: 1 mol. valine (mol.wt. 2,021), i.e. it consists of 15 amino-acid residues. Other observers however, have found a molecular weight about twice as great as this. *Salmin* appears to contain 14 mols. arginine, 3 mols. proline, 3 mols. serine, and 1 mol. valine (21 amino-acid residues, mol.wt. 2,855).

(7) **SCLEROPROTEINS.** These are found mostly in animals where they play the part of skeletal substances, thus performing the function which is undertaken in plants by cellulose. They are insoluble in water and salt solutions. They are digested by pepsin and trypsin. Amongst the scleroproteins are the keratins (substances of hair, feathers, nails, etc.); the collagen of bones, cartilage, and connective tissue, which on heating with water gives gelatin and glue; elastin, the skeletal protein of sinew, and other elastic tissues; fibroin, the protein of silk, etc.

(8) **PHOSPHOPROTEINS.** These contain phosphoric acid as the prosthetic group. They are insoluble in water, but they dissolve in alkalis, and are reprecipitated on addition of acid. Casein from milk, and vitellin from egg-yolk are phosphoproteins.

From casein a mixture of polypeptides containing phosphorus has been obtained, from which a crystalline depeptide phosphate containing serine and glutamic acid can be separated.

(9) **GLUCOPROTEINS.** These contain, as the carbohydrate component, *glucosamine* or the isomeric chondrosamine, substances related to the sugars. They are acidic and are dissolved by alkalis. Members of this group are the mucins (from saliva), mucoids (from cartilage, and egg proteins), and ovalbumin, the chief constituent of egg proteins.

(10) **NUCLEOPROTEINS.** Their prosthetic groups are nucleic acids (see Ch. 62). They are soluble in water, salt solutions, and alkalis, and are weakly acidic. They occur in cell-nuclei, and in viruses.

Section VI. Compounds with three or more functions in the molecule

CHAPTER 19. POLYALCOHOLS

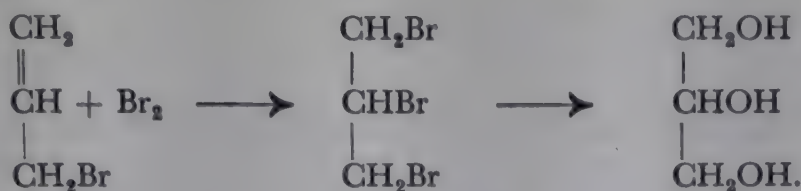
Glycerol,¹ $\text{CH}_2\text{OH} \cdot \text{CHOH} \cdot \text{CH}_2\text{OH}$. The trihydric alcohol glycerol is the basis of natural fats and oils (see p. 213), and the phosphatides, especially lecithin (see p. 218). It is produced as a by-product in alcoholic fermentation (see p. 89), the yield of it being increased, as previously mentioned, by the addition of sulphite. It is present in small amounts in the blood.

Glycerol is obtained technically entirely by the hydrolysis of fats, followed by decolorization by means of animal charcoal, or distillation. During World War I, however, the compound was made in some countries in large quantities by the fermentation of sugar. In normal times, however, this process cannot compete with the hydrolysis of glycerides.

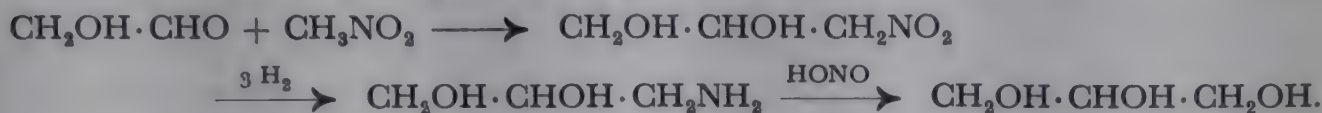
There are several total syntheses of glycerol, which confirm its constitution. 1:2:3-tribromopropane may be used as the starting product, being readily obtained, for example, from allyl bromide and bromine, or by other methods. Its halogen atoms are replaced

¹ JAMES A. LAWRIE, *Glycerol and the Glycols*, New York, (1928).

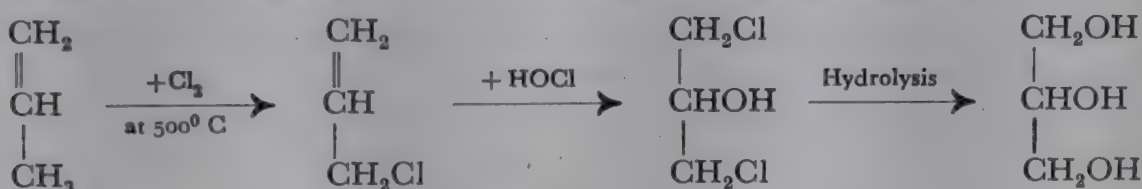
by hydroxyl groups by boiling with water, or by means of potassium acetate in the usual way (Friedel and Silva):



Another synthesis starts from glycolaldehyde (A. Pictet). This is condensed with nitromethane and the nitro-group of the product is replaced by hydroxyl:



Finally an interesting process must be mentioned that has been technically developed by the mineral oil industry in recent years (Groll and Hearne). It starts from propylene obtained from cracking gases. If the propylene is treated with chlorine, then addition to the double bond occurs in the usual way. At high temperatures, however, the reaction may be conducted in such a way that, instead of addition (propylene dichloride is no longer stable at 400–500°), substitution occurs which takes place at the carbon atom having the single bond. Allyl chloride is thus produced, which can be further converted in the usual way through the two dichlorohydrins (according to Lennart Smith circa 70% α,β - and circa 30% α,α' -dichlorohydrin are formed) into glycerol:



Glycerol, of which the discovery and investigation go back to Scheele, Chevreul, Pelouze, Berthelot, and Wurtz, is a transparent, oily liquid, with a sweet taste. It is miscible with water in all proportions, and is very hygroscopic. It boils at 290°. Perfectly pure glycerol solidifies to crystals on thorough cooling and then melts at 17°.

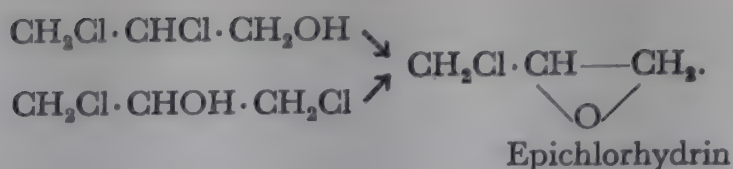
As a trihydric alcohol, glycerol is capable of forming mono-, di-, and triesters and ethers, of which the mono- and diacyl derivatives, as well as the corresponding ethers, can exist in structural isomeric forms. The various esters of glycerol with the halogen hydracids are important in syntheses; they are usually called simply *chlorhydrins*, *bromhydrins*, etc. The two possible *monochlorhydrins* are formed together when glycerol is saturated with hydrogen chloride and the mixture is heated; the α -form predominates:



Of the *dichlorhydrins*, the 1:2-dichloro-compound is easily obtained by the addition of chlorine to allyl alcohol. It is called β -dichlorhydrin. The isomeric 1:3-dichloropropanol-(2), or α -dichlorhydrin, is formed together with other products, by boiling a mixture of glycerol and glacial acetic acid saturated with hydrogen chloride:

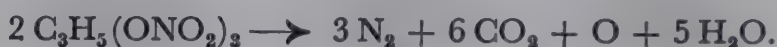


Both dichlorhydrins are converted by means of alkali into *epichlorhydrin* the cyclic anhydride of α -monochlorhydrin:



The ethylene oxide ring in epichlorhydrin is opened in the same easy way as in ethylene oxide itself (see p. 244) by the most diverse reagents. The compound is therefore a valuable product for the preparation of glycerol derivatives.

The five possible mono-, di-, and trinitric esters of glycerol are also known. The trinitrate, usually called simply *nitroglycerine*¹, is important in the manufacture of explosives. The compound is prepared by adding glycerol to a mixture of concentrated sulphuric acid and fuming nitric acid between 10° and 20°, and separates as an oil by pouring the reaction mixture into water. In the pure state it is colourless and odourless. Its vapour produces headaches and is poisonous. Whilst nitroglycerine on ignition burns without explosion, it detonates violently on shock. It breaks down into nitrogen, carbon dioxide, oxygen, and water vapour:

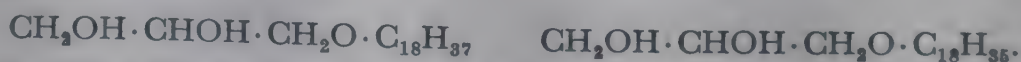


The fact that it is a liquid makes its direct use as an explosive troublesome. Nobel therefore brought it into a solid form by absorbing it in kieselguhr, and it soon became one of the most important explosives, under the name *dynamite*. In itself, dynamite is not very dangerous; it burns without explosion and is also difficult to explode by striking it. On the other hand if detonators such as mercury fulminate or lead azide are used with the dynamite the whole mass explodes. Later, the place of dynamite was partly taken by *Blasting Gelatine*, a tough, jelly-like substance, which is obtained by dissolving about 7 per cent of nitrocellulose in nitroglycerine. It possesses similar explosive properties to dynamite. *Gelatine Dynamite* is composed of slightly gelatinized nitroglycerine mixed with 30–60 % ammonium or sodium nitrate and small quantities of other substances. A further important use for nitroglycerine is in the gelatinization of gun-cotton.

The α - and β -glycerophosphates are found in lecithin (see p. 218) and other phosphatides, and can also be made synthetically. The α -form is known in the optically active state.

Glycerides of the higher fatty acids, the fats and oils, have already been dealt with on p. 213 ff.

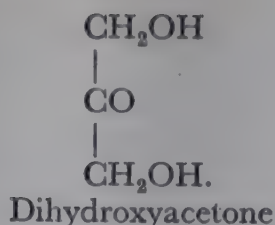
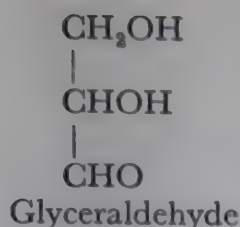
Glyceryl ethers are contained in the unsaponifiable portions of the oil of shark (*Elasmobranchii*). Thus, according to Heilbron, *batyl alcohol* is α -octadecyl glyceryl ether and *selachyl alcohol* is α -oleyl glyceryl ether (optically active with the configuration of D-glyceraldehyde):



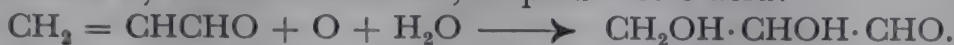
Batyl alcohol has also been isolated from bone-marrow, the aorta, the spleen, etc., of mammals.

Considerable importance attaches to the first oxidation products of glycerol. By the use of mild oxidizing agents, it is possible to carry out the reaction so that only one alcohol group, the primary or the secondary, is oxidized. *Glyceraldehyde* and *dihydroxyacetone* are formed. These compounds are the simplest aldose and ketose, respectively, and are the forerunners of the carbohydrates:

¹ R. ESCALES, *Nitroglycerin und Dynamit*, Berlin.



The mixture of the two substances which is obtained when the oxidation is carried out with hydrogen peroxide and ferrous salts, platinum black and atmospheric oxygen, nitric acid, bromine and sodium carbonate, etc., is known as *glycerose*. The aldehyde predominates in the mixture. Dihydroxyacetone itself is the sole product of the oxidation of glycerol by the *sorbose bacterium*, which, as has been mentioned elsewhere, exclusively attacks secondary hydroxyl groups. To prepare glyceraldehyde, a suitable method is the oxidation of acrolein with chlorate activated by osmium tetroxide, or perbenzoic acid:



Strong nitric acid converts glycerol into *glyceric acid*:

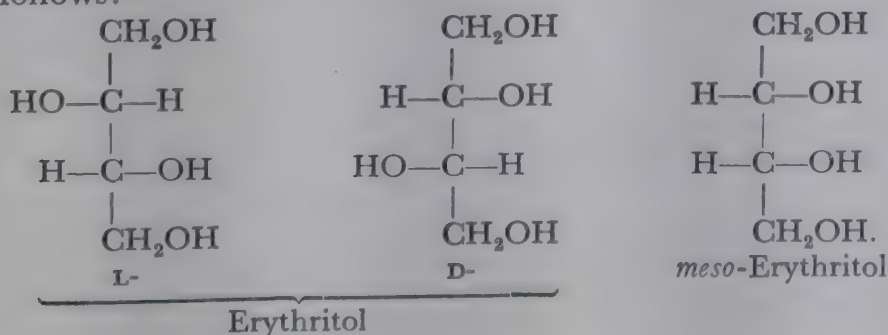


This is an oily liquid, soluble in water and alcohol, but insoluble in ether. The synthetic substance is, of course, inactive, but can be resolved into the optically active forms. The salts of the glyceric acid, which is dextrorotatory in aqueous solution, are themselves lævorotatory. This glyceric acid corresponds as far as configuration is concerned to L(+)-lactic acid (sarcolactic acid) and L(—)-malic acid (see p. 303).

Glycerol is completely absorbed and used up by the organism. On account of its sweet taste and its preserving power it is often used in foodstuffs and beverages. Its greatest technical use is in the manufacture of nitroglycerine. In pharmacy and cosmetics it is used as a foundation for ointments and pastes, for the treatment of cracked skin, etc. In hydraulic brakes and presses it is used as an highly viscous brake fluid. Gas-meters are filled with it. Use is made of its non-drying properties when it is added to plastics, copying-inks, stamping-inks, and printing-inks. Finally, glycerol is used in the textile industry as a finisher.

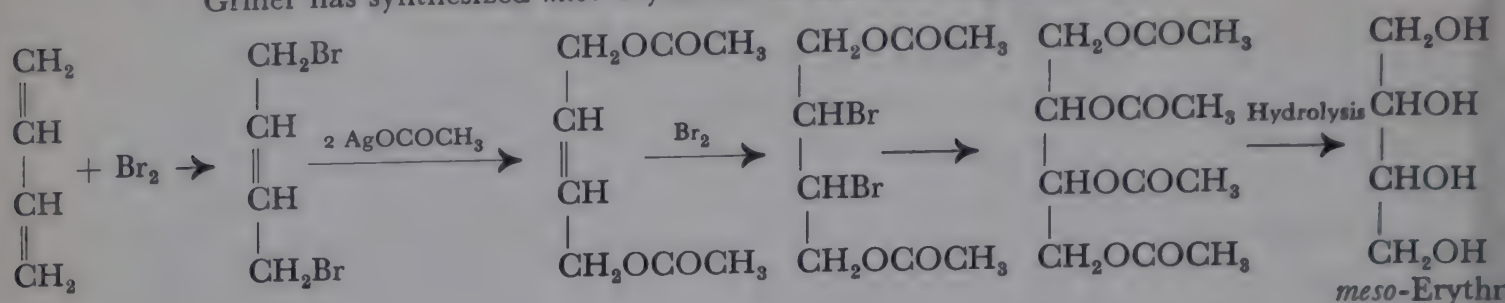
Erythritol, $\text{CH}_2\text{OH} \cdot \text{CHOH} \cdot \text{CHOH} \cdot \text{CH}_2\text{OH}$. This tetrahydric alcohol contains two structurally identical, asymmetric carbon atoms. For compounds of this kind theory predicts (p. 107) three spatial isomers: two optically active, enantiomorphic forms, and an internally compensated, inactive compound, which cannot be resolved. These three isomerides are known, and are called D-, L-erythritol, and meso-erythritol.

As regards the space formula of inactive meso-erythritol there can be no doubt. In the case of the active erythritols the formulæ can be assigned on the basis of their relationships with the tartaric acids (see p. 334). D-Erythritol can be oxidized to D-tartaric acid, and L-erythritol to L-tartaric acid. The projection formulæ are therefore as follows:

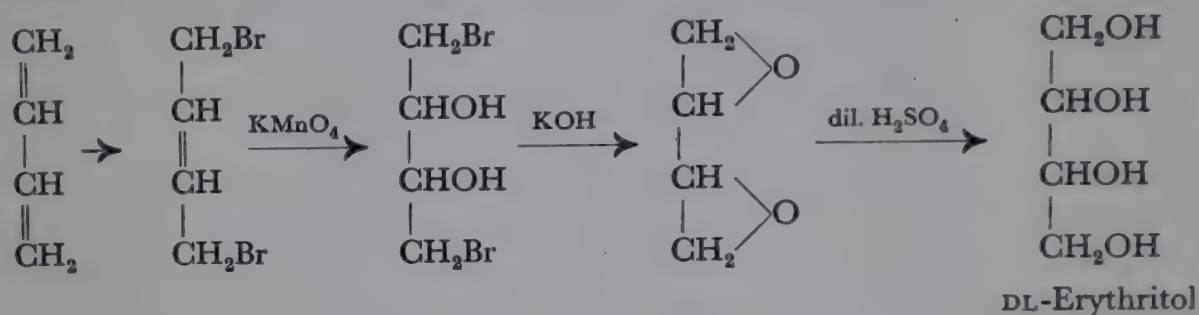


Only *meso*-erythritol is found in nature, in the free form in algæ, but more particularly esterified with diorsellinic acid, or lecanoric acid, (see Ch. 41, section 2) in lichens (*Rocella*). The compound is called *erythrin*.

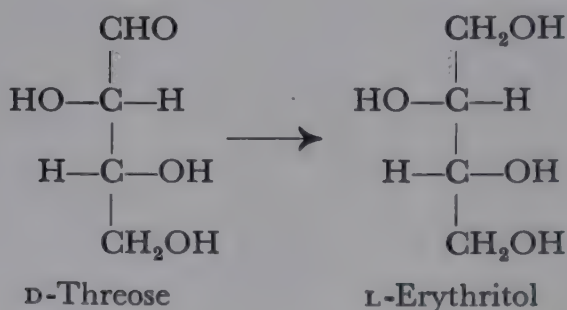
Griner has synthesized *meso*-erythritol in the following manner:



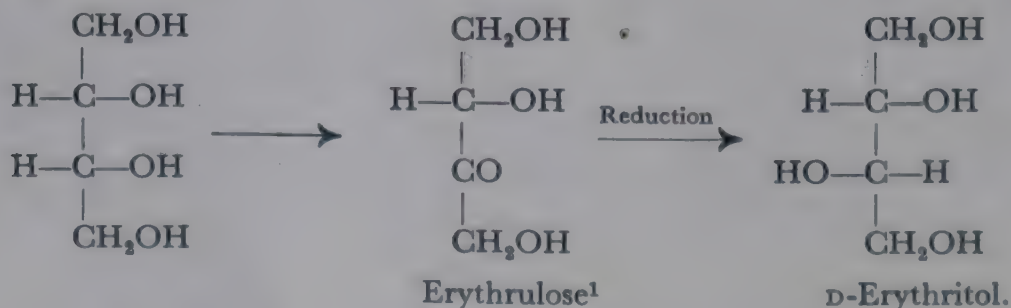
Racemic DL-erythritol can also be obtained from butadiene. The synthesis proceeds via 1:4-dibromobutene-2, then an erythritol dibromohydrin is formed, and erythritol dioxide:



Moreover, it has been possible to devise methods of making the active forms artificially. L-Erythritol (dextrorotatory) was prepared by Maquenne and by Ruff by reduction of D-threose:



and the antipode from *meso*-erythritol, the latter being oxidized by the sorbose bacterium to the ketose *erythrulose*, which, on reduction with sodium amalgam gave D-erythritol in addition to *meso*-erythritol:



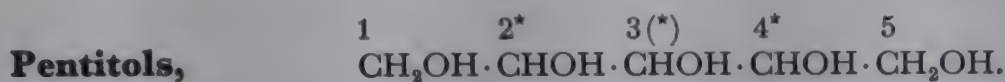
meso-Erythritol tastes sweet, is easily soluble in water, but difficultly in alcohol. It boils at 329°, and melts at 120°.

The active erythritols melt at 89°, and DL-erythritol at 72°. D-Erythritol is laevorotatory in water ($[\alpha]_D = -4.4^\circ$), but dextrorotatory in alcohol ($[\alpha]_D = +11.1^\circ$). (More recently it has been proposed to call L-erythritol, D-threitol.)

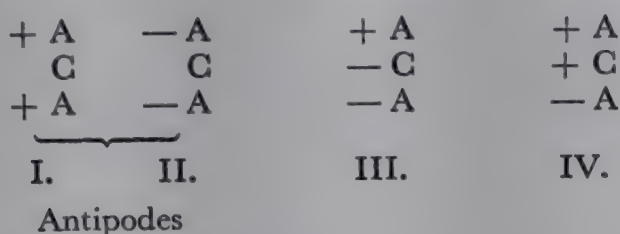
¹ The configuration of erythrulose has been chosen arbitrarily.

Polyhydric alcohols are characterized by the ending *-itol*. The erythritols are *tetritols*.

Pentaerythritol, $C(CH_2OH)_4$. This tetrahydric alcohol with a branched carbon chain is formed by the continued action of lime water on a mixture of formaldehyde and acetaldehyde. The mechanism of the reaction is unknown. The compound has recently become of technical importance as its tetranitrate is a very useful explosive ("PETN", "Nitropenta", "Pentrite", "Pentaryt", "Pentyl").



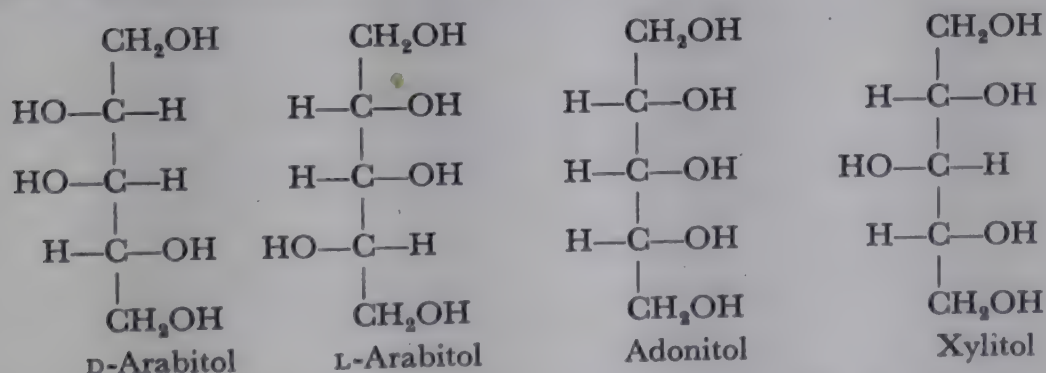
For compounds of the pentitol type which contain two structurally identical asymmetric carbon atoms (2 and 4) separated by a third carbon atom to which are attached in addition two different groups, the following possibilities of isomerism can be predicted (A stands for the radical $CH_2OH\overset{*}{CHOH}-$):



The first two forms are ordinary antipodes; their molecules are non-superimposable mirror-images. They must therefore be optically active. Their middle carbon atom C is neither structurally nor stereochemically asymmetric.

It is different for the two isomerides III and IV. The middle carbon atom is indeed also combined with two structurally identical radicals A, but these are, from the stereochemical point of view, different, one possessing a +, the other a — configuration. There is, therefore, the possibility of the existence of two isomeric forms, which differ in the configuration of the middle carbon atom. Both are optically inactive, since their molecules are symmetrical. Carbon atoms which have attached to them structurally identical, but stereochemically different radicals are said to be *pseudoasymmetric*.

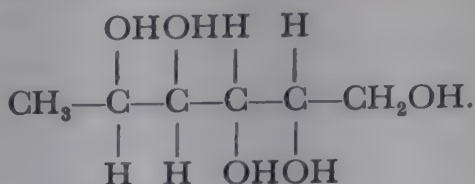
The two active and the two non-resolvable inactive pentitols, as predicted by theory, as well as the racemate of the first two, are known:



Adonitol occurs naturally in *Adonis vernalis*. It melts at 102° . It is optically inactive (E. Fischer).

Xylitol has been obtained by the reduction of xylose, and D- and L-*arabitol* in the same way from D- and L-arabinose, respectively. D-Arabitol is found, for example, in lichens and in the fungus *Boletus bovinus*. The arabitols melt at 103° and are so weakly optically active that their rotation is only observable after the addition of borax.

By the reduction of methylpentoses, methylpentitols have been prepared; thus the active *rhamnitol* from *rhamnose*:



In the hexitols there are two pairs of structurally similar, asymmetric carbon atoms (2 and 5, and 3 and 4). This gives the possibility of 10 stereoisomeric forms. Most of these are known and have been obtained by the reduction of the corresponding aldoses or ketoses. Their configurations will be presented in connection with those of the hexoses. Only those hexitols which occur naturally will be mentioned here.

D-MANNITOL. This substance is very widely spread in nature. It forms the chief constituent of the so-called manna (Proust), the solidified sap of the manna tree and similar plants, which is obtained by making an incision in the tree. Mannitol has also been detected in fungi, celery, olives, jasmine, algæ, and many other plants. It is also a normal constituent of urine, and is formed from some kinds of sugar by fermentation processes. It melts at 165–166°, and boils at 276–280° (1 mm). Its rotation in aqueous solution only amounts to $[\alpha]_D = -0.25^\circ$. Mannitol may be obtained synthetically by the reduction of mannose (see p. 346) or fructose (see p. 346), and it can be converted into them by mild oxidation. There is a number of internal anhydrides derived from mannitol which, however, cannot be considered here.

D-SORBITOL is contained in many fruits, especially in the berries of the mountain ash (Boussingault) from which the compound can be suitably obtained. D-Sorbitol melts when anhydrous at 110–111°, and is lævorotatory in aqueous solution ($[\alpha]_D = -1.73^\circ$). The sorbose bacterium oxidizes it to a ketose, sorbose (see p. 347) (Bertrand).

D-IDITOL occurs together with sorbitol in the berries of the mountain ash. It can be separated from sorbitol by means of the sorbose bacterium which does not attack it. It has been obtained synthetically by the reduction of sorbose and idose (see p. 337) (E. Fischer). It melts at 73°. In water it is lævorotatory ($[\alpha]_D = -3.50^\circ$).

DULCITOL. This compound is obtained from manna from Madagascar, which consists almost entirely of dulcitol. It has also been detected in other plants. It is made artificially by reduction of galactose. It melts at 188°, and is optically inactive and non-resolvable (meso form).



PERSEITOL. This heptitol is found in the fruits and leaves of *Laures persea* (Muntz, Maquenne) and has been obtained from mannose through mannose cyanhydrin and mannoheptose (see synthesis of sugars). It melts at 188°. No rotation can be detected in aqueous solution, but after the addition of borax the solution becomes dextrorotatory.

VOLEMITOL (identical with α -sedoheptitol), is found in floating moulds, in the

roots of *Primulaceæ* (Bourquelot), and in lichens. It melts at 155°. In aqueous solution it is dextrorotatory, $[\alpha]_D = +2.65^\circ$.

In certain species of chestnut there is a polyhydric alcohol, $C_8H_{18}O_7 \cdot H_2O$, castanitol, which is probably a methylheptitol. M.p. 164°.

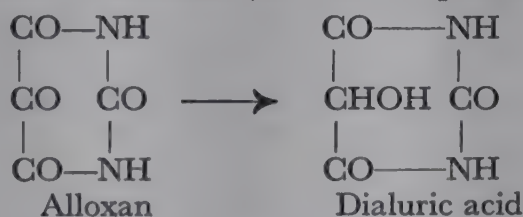
CHAPTER 20. OXIDATION PRODUCTS OF POLYHYDRIC ALCOHOLS (WITH THE EXCEPTION OF THE TRUE CARBOHYDRATES)

In this chapter will be considered a number of compounds which are related to the true carbohydrates and their transformation products, but, being the simplest polybasic hydroxy-acids occurring in nature, are at the same time more closely connected with each other.

Tartronic acid, $HOOC \cdot CHOH \cdot COOH$. This hydroxymalonic acid is difficult to prepare. It is formed in small quantities by the oxidation of glycerol with potassium permanganate, and also by the removal of bromine from bromomalonic ester by means of silver oxide:

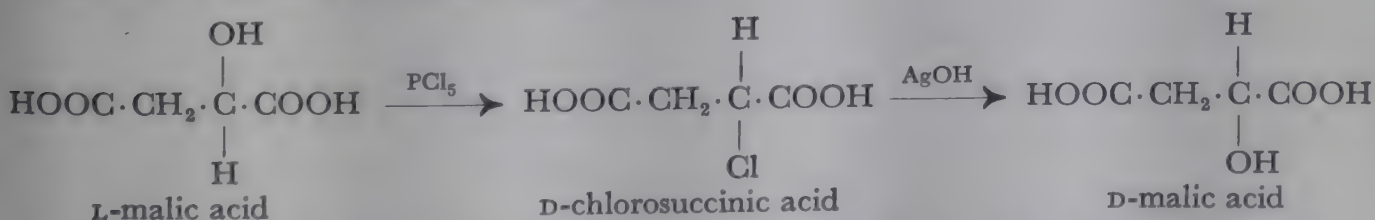


It melts at 156–158°. Its ureide is *dialuric acid* (tartronylurea), which is best prepared by the reduction of alloxan (see Ch. 62, purine compounds):



Malic acid, $HOOC \cdot CHOH \cdot CH_2 \cdot COOH$. Malic acid contains an asymmetric carbon atom and is therefore known in two active forms and a racemic form. L(—)-*Malic acid* is widely found in nature. It occurs in numerous fruits, particularly in the berries of the mountain ash, and the berries of *Berberis vulgaris*, also in rhubarb stems, in the fruits of *Hippophae rhamnoides*, and in wine. The berries of the mountain ash and barberry are used to obtain the compound.

D(+)-*Malic acid* is obtained by reduction of D-tartaric acid with hydrogen iodide. D-*Malic acid* can, however, also be obtained from L-malic acid by making use of the Walden inversion, as follows:

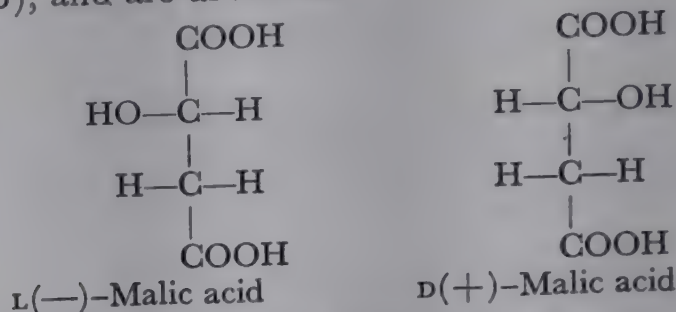


Finally, the *racemic form* is produced, for example, by the addition of water to maleic and fumaric acids, from DL-tartaric acid (racemic acid) by reduction, and from DL-bromosuccinic acid by replacement of the bromine atom by hydroxyl. These various syntheses give at the same time a proof of the constitution of the

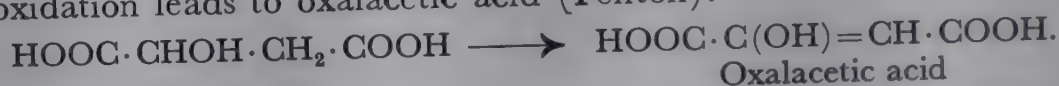
compound, which is supported by the reduction of malic acid to succinic acid.

The melting point of racemic malic acid is $130-131^{\circ}$, and that of the active forms is 100° . The optical rotation depends on the concentration of the solution. Dilute solutions of L-malic acid rotate the plane of polarization to the left; this l  vorotation decreases, however, with increasing concentration and becomes zero at a concentration of 34 %. Solutions stronger than this rotate the plane to the right.

The configurations of these two active malic acids have been, arbitrarily chosen (see p. 333), and are as follows:

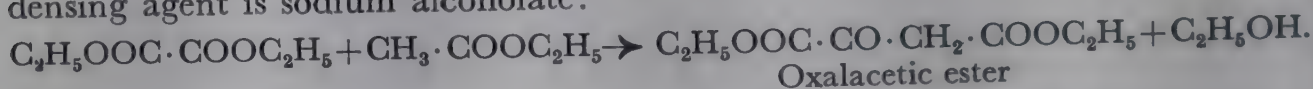


In connection with the chemical properties of malic acid it will be recalled that it gives maleic anhydride on heating, and succinic acid on reduction. Controlled oxidation leads to oxalacetic acid (Fenton):



Malic acid is used in medicine as a constituent of purgatives and in preparations for the relief of sore throat.

Oxalacetic acid, $\text{HOOC} \cdot \text{C}(\text{OH})=\text{CH} \cdot \text{COOH}$. Oxalacetic acid, as mentioned above, is an oxidation product of malic acid. Its ester is formed very smoothly by the "ester condensation" of oxalic ester and acetic ester. The condensing agent is sodium alcoholate:



For the compound a keto form and an enol form come into consideration:



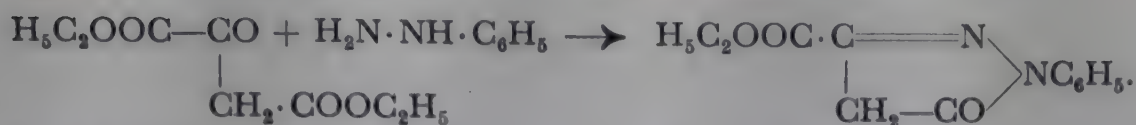
Titration with bromine and the results of refractometric determinations show that *liquid oxalacetic ester* [a thick, colourless oil, b.p. $131-132^{\circ}$ (24 mm)] is a mixture of the two desmotropic forms, in which the enol form predominates (about 80 per cent).

The two oxalacetic acids known are completely enolized and are obtained by hydrolysing hydroxymaleic anhydride under certain conditions (Wohl). They are crystalline solids (melting point 152° and 184° , respectively), and are to be considered as *cis-trans* isomerides:

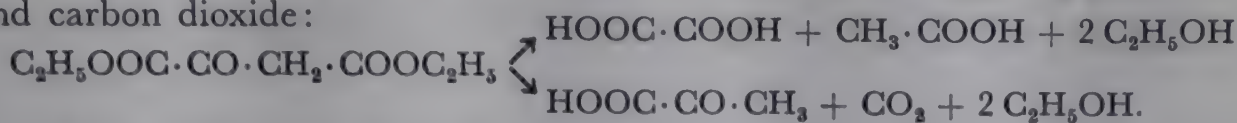


They may therefore be regarded as hydroxymaleic and hydroxyfumaric acid, respectively.

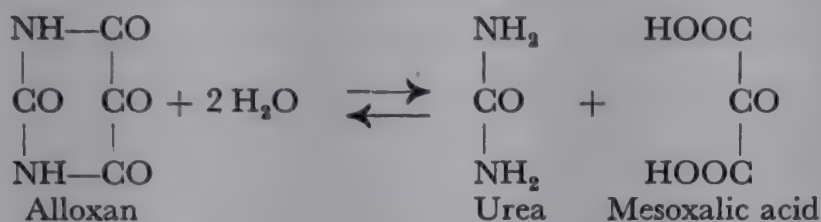
Oxalacetic ester is a valuable product for many syntheses. As a β -keto-acid it shows a reactivity similar to that of acetoacetic ester and reacts, for example, with phenylhydrazine to give a pyrazolone derivative:



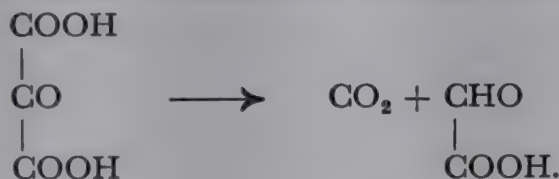
By the action of alkalis it can undergo either an "acid" hydrolysis, breaking down into oxalic and acetic acids, or a "ketonic" hydrolysis, giving pyruvic acid and carbon dioxide:



Mesoxalic acid, $\text{HOOC}\cdot\text{CO}\cdot\text{COOH}$. Mesoxalic acid and its hydrate, $\text{HOOC}\cdot\text{C}(\text{OH})_2\cdot\text{COOH}$, are of interest on account of their relationship to uric acid. The ureide of mesoxalic acid, *alloxan*, is an important degradation product of uric acid, and gives mesoxalic acid and urea on hydrolysis. On the other hand, it can itself be formed from urea and mesoxalic acid:

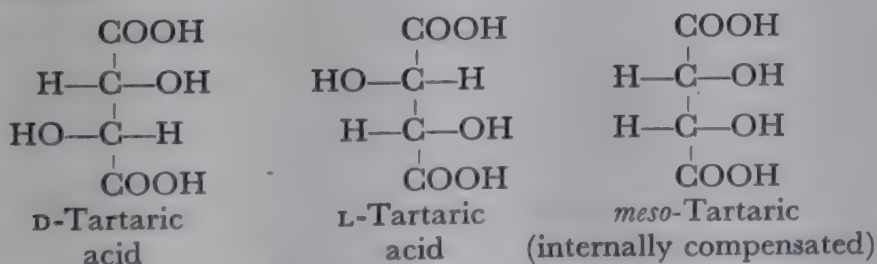


Mesoxalic acid melts at 121° . It is an α -keto-acid and can therefore reduce ammoniacal silver nitrate solution. It decomposes on boiling with water into carbon dioxide and glyoxylic acid:



The existence of the hydrated form is remarkable. Its stability is evidently to be ascribed to the influence of the negative carboxyl group adjacent to the carbonyl group (cf. chloral, glyoxylic acid).

Tartaric acids, $\text{HOOC}\cdot\overset{*}{\text{CHOH}}\cdot\overset{*}{\text{CHOH}}\cdot\text{COOH}$. The tartaric acids are constructed according to the same stereochemical type as erythritol, i.e. they contain two structurally identical asymmetric systems. Like erythritol the substance must therefore occur in four isomeric forms, a *dextro*- and a *levorotatory* form, the corresponding *racemate*, and a *meso* form. The choice of configurational formulæ for the active tartaric acids may be made on the basis of their relationships with the sugars (see p. 333-334) and with malic acid, the following formulæ being obtained:



DL-Tartaric acid is known as *racemic acid*.

It was with the tartaric acids that Pasteur carried out his pioneer researches on the resolution of racemic compounds. He observed the spontaneous resolution of the sodium ammonium salt of racemic acid below 27° , in which temperature range the conglomerate is stable, whilst above 27° , the racemate crystallizes as a whole. He discovered the biochemical method of resolution, by destroying the

D-component of racemic acid by means of moulds (*Penicillium glaucum*, *Aspergillus niger*), L-tartaric acid being left behind. Finally, he discovered the chemical method of resolution, when he resolved racemic acid into its enantiomorphs by the use of cinchonine and other alkaloids.

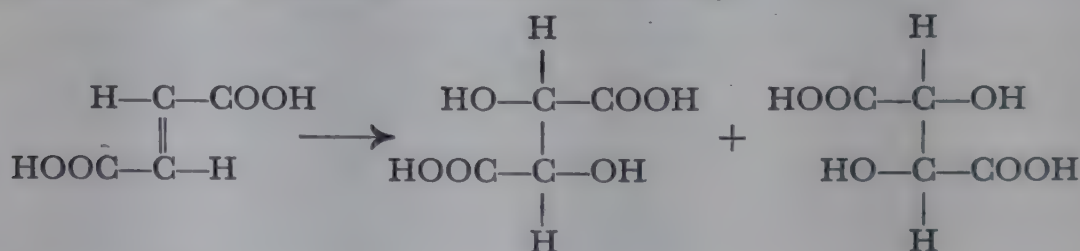
D-Tartaric acid occurs naturally. It is contained in many fruits, partly in the free state, and partly in the form of salts. In the fermentation of wine, the increasing alcohol content causes acid potassium tartrate, cream of tartar, to crystallize out. It is deposited in the form of hard crusts on the walls of the vessel, and is the principal source for the technical preparation of D-tartaric acid.

The acid forms large, transparent crystals, readily soluble in water and alcohol. It melts at 170°. Its aqueous solution rotates the plane of polarization to the right, but the rotation decreases with increasing concentration and as the temperature is lowered; the super-saturated, cold solution is levorotatory. The salts of D-tartaric acid and its esters are also dextrorotatory.

When partially reduced, D-tartaric acid gives D-malic acid. Energetic reduction with hydrogen iodide converts it into succinic acid. It is very sensitive to oxidizing agents, and gives a silver mirror with an ammoniacal solution of a silver salt. It is converted by strong oxidizing agents into oxalic acid. It is photochemically oxidized in the presence of uranium salts to glyoxal, and by hydrogen peroxide and ferrous salts to dihydroxymaleic acid.

The rearrangement which D-tartaric acid undergoes on boiling with alkalis, water, or dilute acids is important. It is thus converted into the inactive, non-resolvable *meso-tartaric acid*. This melts at 140°. To separate the latter from the active and racemic tartaric acids, use is made of the fact that its acid potassium salt, unlike cream of tartar, is readily soluble in cold water.

L-Tartaric acid resembles, of course, the D-form in its chemical and physical properties. It is prepared by the resolution of *racemic acid*. To obtain the latter several syntheses are available, e.g. the oxidation of fumaric acid (maleic acid gives mesotartaric acid under the same conditions):



or from glyoxal by the cyanhydrin synthesis:



Practically, the most suitable method is the artificial racemization of D-tartaric acid, which can be brought about by boiling with alkalis. However, large amounts of mesotartaric acid are formed at the same time.

The melting point of anhydrous racemic acid is 204°. It crystallizes from water with one molecule of water of crystallization.

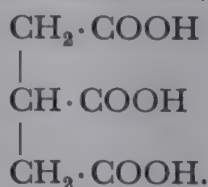
D-Tartaric acid is used in industry as an addition to printing colours, and as a mordant. It is frequently used in lemonade powders. Tartrates find a fairly considerable application. *Cream of tartar*, the acid potassium salt, is used as a baking powder and in dyeing as an addition to the dye-bath. *Tartar emetic*, potassium antimonyl tartrate, $(\text{SbO})\text{OOC}\cdot\text{CHOH}\cdot\text{CHOH}\cdot\text{COOK}, \frac{1}{2}\text{H}_2\text{O}$, is used in dyeing as a mordant, and in medicine as an emetic and in combating infectious diseases.

Several heavy metals give complex salts with alkali tartrates. Of practical importance

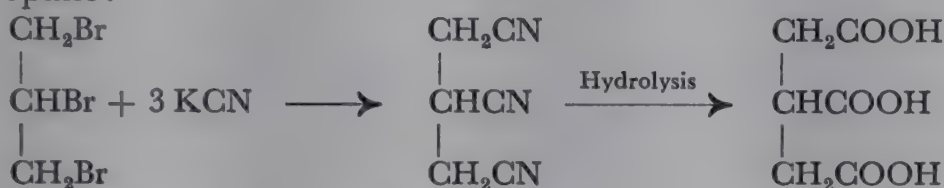
are those of copper which are formed when copper salts are added to an alkaline solution of a tartrate. Copper hydroxide is not precipitated under these conditions, but a dark blue, clear solution is formed. Fehling's solution, which is much used for the detection of reducing substances (particularly sugars) is made by dissolving 34.6 g of $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ in 500 c.c. of water, and 173 g of crystalline sodium potassium tartrate (*Rochelle salt*) and 60 g of sodium hydroxide in another 500 c.c. of water. When required for use equal volumes of the two solutions are mixed. Reducing substances precipitate cuprous oxide from it. The quantity precipitated can be used as a measure of the reducing power of the substance added.



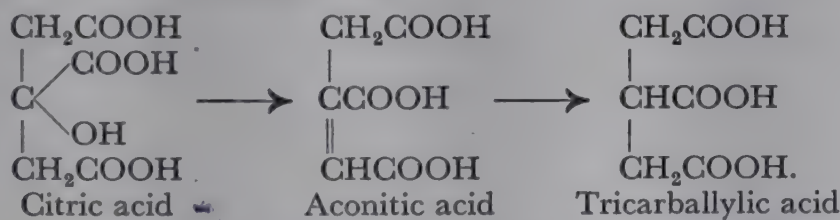
Citric acid, $\text{HOOC} \cdot \text{CH}_2 \cdot \text{C}(\text{OH}) \cdot \text{CH}_2 \cdot \text{COOH}$. Citric acid is the β -hydroxy-derivative of propane- α, β, γ -tricarboxylic acid, or *tricarballic acid*:



The constitution of this compound follows from its synthesis from α, β, γ -tribromopropane:



Tricarballic acid is connected with citric acid through *aconitic acid* (see p. 284) which is obtained by eliminating water from citric acid, and which can easily be reduced to tricarballic acid:

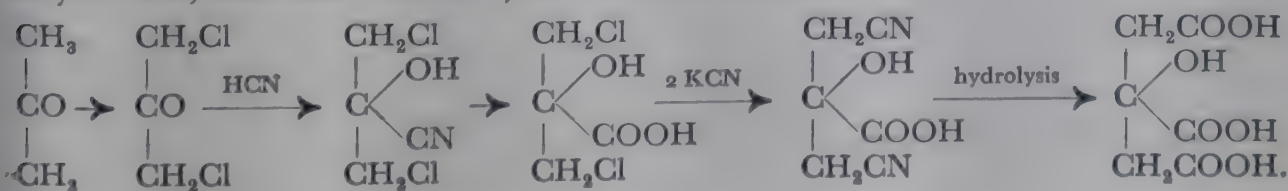


The melting point of tricarballic acid is 165° . Its calcium salt, which is more soluble in cold water than in hot, has been detected in evaporated beet juice.

Citric acid is one of the most widely spread plant acids. It was discovered in lemon juice, in which it occurs very abundantly, and it is obtained from this commercially via the difficultly soluble calcium salt. It also occurs, however, in many other fruits (red-currants, cranberries, mountain ash berries), in beet juice, in wine, etc. It is also present in the human and animal organisms.

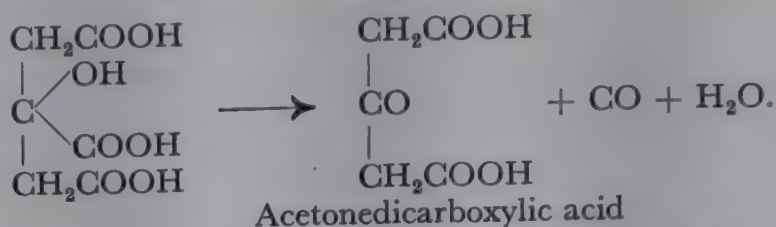
Besides the method of preparing it from the juice of unripe lemons, another method of preparation, starting from carbohydrates (glucose, maltose, dextrins) is of technical interest. These carbohydrates are converted to the extent of 50 per cent into citric acid by certain moulds (*Citromycetes*). The mechanism of this peculiar reaction is not perfectly clear.

The constitution of citric acid is arrived at from its relationship with tricarballic acid, and also from its synthesis from acetone:



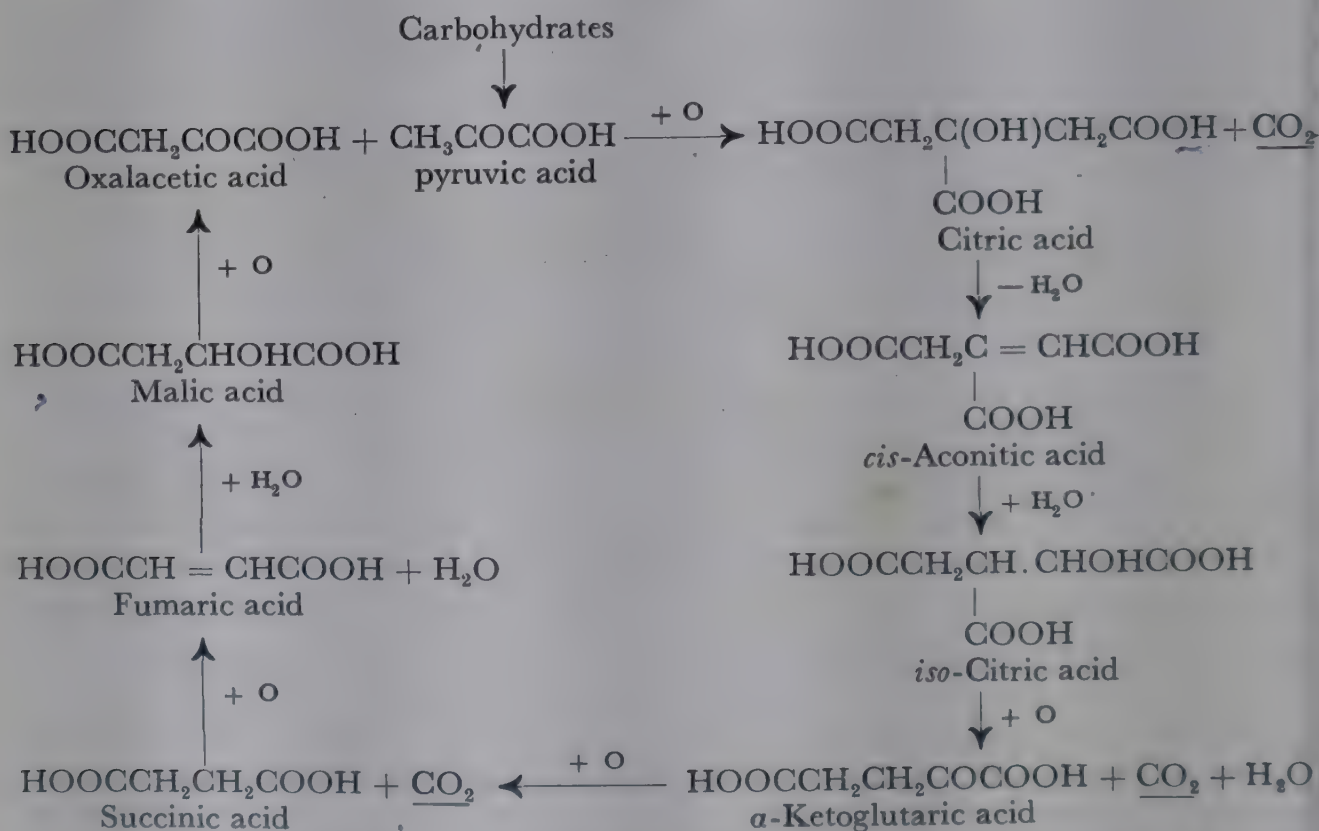
Citric acid is known in a hydrated form ($1 \text{ H}_2\text{O}$) as well as in the anhydrous state. The latter melts at 153° , the hydrate at about 100° . It is very readily soluble in water.

The decomposition of the acid into citraconic and itaconic acids on heating has already been referred to on p. 284. A very important decomposition of citric acid is that which occurs with concentrated sulphuric acid. Like other α -hydroxy-carboxylic acids and α -keto-acids it loses carbon monoxide and water (or formic acid), and is converted into *acetonedicarboxylic acid*:



The latter product is valuable in various syntheses (cf. for example, that of ecgonine), for its two methylene groups between carbonyl groups possess equally great and diverse reactivity as those of acetoacetic ester and malonic ester, and are therefore suited for condensation reactions.

In the metabolism of animal cells, and probably also in yeast and other micro-organisms, citric acid plays an important part. Hence the term "citric acid cycle", through which the degradation of the carbohydrates may take place. The following survey shows the individual members of this cycle:



By this sequence of reactions, 1 mol pyruvic acid has thus been oxidized to 3 mols of CO_2 and 2 mols of H_2O , which, as shown by the total equation



requires 5 atoms of oxygen.

Citric acid is used commercially as an addition to lemonades, fruit bonbons, pharmaceutical preparations, as a substitute for vinegar, and particularly in colour printing, where it is added to the dye solution, and is also used as a reserve.

CHAPTER 21. CARBOHYDRATES¹

The term *carbohydrates* goes back to a time when it was thought that all compounds of this group contained the elements carbon, hydrogen, and oxygen in the same proportions as various hydrates of carbon, thus corresponding to the general composition $C_n(H_2O)_m$. Apart from the fact that this view appears to-day to be much too formal, later investigations have brought to light several substances which, according to their chemical nature, must be regarded as carbohydrates, yet deviate from the above-mentioned general type in composition (e.g. the methylpentoses, the methylhexoses, and the desoxy-sugars). Modern investigation puts all those substances which have the characteristics of sugars or resemble them in structure and chemical behaviour in the class of carbohydrates.

The general properties of the carbohydrates differ, however, frequently from substance to substance; between the easily water-soluble, sweet-tasting glucose, the colloidal, paste-forming starch, and the completely insoluble cellulose, there appear to be enormous differences. Yet chemical degradation shows that they have nevertheless a common basis, since starch and cellulose can be broken down in different ways to glucose.

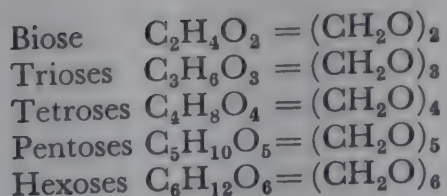
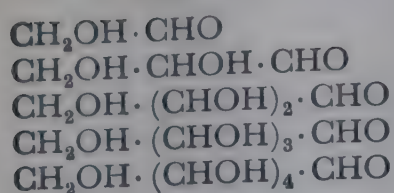
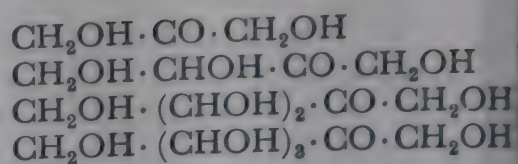
It is convenient to classify the carbohydrates into the following groups:

1. MONOSACCHARIDES, or simple sugars (e.g. glucose, fructose).
2. OLIGOSACCHARIDES (Simpler polysaccharides). These are built up of monosaccharides and resemble them fairly closely in solubility, taste, and chemical properties. To this class belong cane sugar (sucrose), malt sugar (maltose), and milk sugar (lactose), etc.
3. POLYSACCHARIDES. These are also condensation products of simple sugars, but are not soluble in water, forming, at most, colloidal solutions. Their other properties also differ considerably from those of the simple sugars. Examples are starch, glycogen, cellulose.

I. Monosaccharides

The monosaccharides are, according to their chemical nature, *hydroxyaldehydes* or *hydroxyketones*, which contain a hydroxyl-group adjacent to a carbonyl group. The former are called *aldoses*, the latter *ketoses*. According to the number of oxygen atoms present in the molecule they are called *bioses*, *trioses*, *tetroses*, *pentoses*, *hexoses*:

¹ Bibliography: A. W. VAN DER HAAR, *Anleitung zum Nachweis, zur Trennung und Bestimmung der reinen und aus Glykosiden usw. erhaltenen Monosaccharide und Aldehydsäuren*, Berlin, (1920). — J. BÖESEKEN, *Configuration of the Saccharides*, Leiden, (1925). — I. I. L. VAN RIJN, *Die Glycoside*. Chemische Monographie der Pflanzenglycoside. 2nd ed. by Hugo Dieterle, Berlin, (1931). — HANS VOGEL und ALFRED GEORG, *Tabellen der Zucker und ihrer Derivate*, Berlin, (1931). — HEINZ OHLE, *Die Chemie der Monosaccharide und der Glykoside*, Munich, (1931). — W. N. HAWORTH, *Constitution of Carbohydrates*, London, (1932). — E. FRANKLAND ARMSTRONG and K. F. ARMSTRONG, *The Glycosides*, 2nd ed., New York, (1934). — B. TOLLENS and HORST ELSNER, *Kurzes Handbuch der Kohlenhydrate*, 4th ed., Leipzig, (1935). — FRITZ MICHEEL, *Chemie der Zucker und Polysaccharide*, Leipzig, (1939). — W. W. PIGMAN and M. L. WOLFROM, *Advances in Carbohydrate Chemistry*, New York, (1945). WILLIAM WARD PIGMAN and RUDOLPH MAXIMILIAN GOEPP JR., *Chemistry of the Carbohydrates*, New York and London, (1948). — JOHN HONEYMAN, *An Introduction to the Chemistry of Carbohydrates*, Oxford and London, (1948).

Aldoses:*Ketoses:*

A compound $\text{CH}_3(\text{CHOH})_4 \cdot \text{CHO}$, would not be called a hexose, in spite of the fact that it contains six carbon atoms, but a *methylpentose*, since it contains only five oxygen atoms.

The aldoses and ketoses shown above can all be regarded as polymers of formaldehyde, $(\text{CH}_2\text{O})_x$. This relationship is more than formal. It will be seen later that it is possible to produce monosaccharides by the polymerization of formaldehyde.

With the exception of the simplest aldose, glycolaldehyde, and the simplest ketose, dihydroxyacetone, all monosaccharides have one or more asymmetric carbon atoms and must, therefore, occur in stereoisomeric forms. In the case of the aldohexoses, $\text{CH}_2\text{OH} \cdot (\text{CHOH})_4 \cdot \text{CHO}$, containing four asymmetric carbon atoms, there should be $2^4 = 16$ different forms. Actually the number is much greater. This is due to tautomerism which plays an important part in the sugar group, but the importance of which has only recently been sufficiently realized.

All naturally occurring monosaccharides possess a normal carbon chain, with only a few exceptions known at present: *apiose*, $\begin{array}{c} \text{CH}_2\text{OH} \\ \text{CH}_2\text{OH} \end{array} \rangle \text{C}(\text{OH}) \cdot \text{CHOH} \cdot \text{CHO}$, also the sugar group in streptomycin, and perhaps also the sugar from the hamamelis tannin, which is regarded as having the formula



OCCURRENCE OF MONOSACCHARIDES. Glucose and fructose are fairly widely spread in nature. They are particularly abundant in sweet fruits. The monosaccharides occur, however, to a much larger extent as constituents of the molecules of oligosaccharides, such as cane sugar and milk sugar, and of polysaccharides, e.g. starch and cellulose. Of all organic substances found in nature, cellulose occurs to the greatest extent.

Another source of monosaccharides is the *glycosides* (see p. 328) which are compounds of sugars with other substances of different structure (e.g. alcohols or phenols). These are exceedingly abundant, especially in plants. Amygdalin, the blue and red colouring matters of blossoms and berries, yellow colouring matters of the flavone series, the digitalis glycosides, and many others belong to this class. Some of them occur to such an extent that they may be used as starting materials for the preparation of some of the rare sugars.

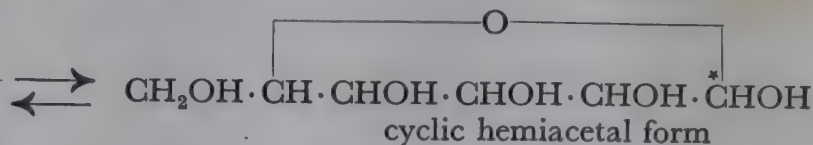
Finally, another type of derivative of the monosaccharides is found in the class of the tannins. In these the alcoholic hydroxyl groups of glucose are esterified with aromatic hydroxy-acids (gallic acid and digallic acids).

PHYSICAL PROPERTIES. The monosaccharides are neutral compounds, readily soluble in water, and difficultly soluble in alcohol. In ether they do not dissolve at all. Many of them taste sweet, yet there are all the degrees of taste from sweetness

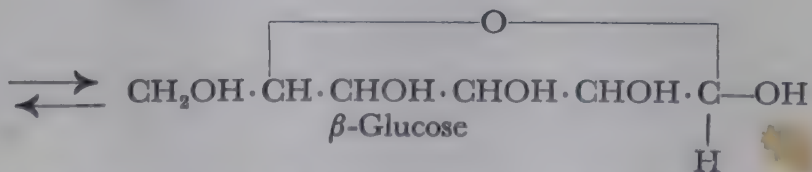
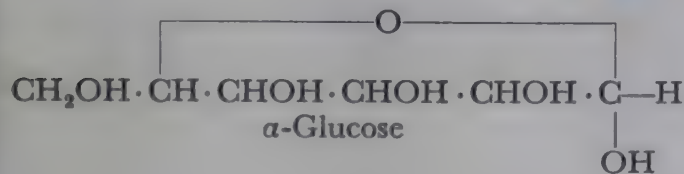
to tastelessness, and to bitterness. On heating they become brown and char.

All naturally-occurring monosaccharides are optically active. Their specific rotation is not only an important constant for their characterization, but also serves for the determination of the concentration of sugar solutions when the sugar itself is known.

The rotation of the monosaccharides in aqueous solution is, however, variable. If it measured immediately after the sugar has been dissolved it is found to increase or decrease and finally to remain constant at a definite value. Thus the specific rotation of ordinary glucose shortly after the solution in water has been made is $[\alpha]_D = +109.6^\circ$. After some hours, the final value is $[\alpha]_D = +52.3^\circ$. The more extensive investigation of this peculiar phenomenon, which was discovered by Dubrunfaut, revealed that every monosaccharide can exist in two forms, called the α - and β -forms (Tanret, Armstrong). The possibility of their formation is due to the fact that the aldoses and ketoses do not exist entirely, or predominantly in the open-chain aldehyde or ketone form, but as cyclic hemiacetals. There is tautomeric equilibrium between the carbonyl and cyclic hemiacetal forms:



On transition from the open-chain molecule to the cyclic molecule, a new asymmetric carbon atom (marked by an asterisk in the formula) makes its appearance. This causes the existence of two isomeric sugars which are *not antipodes* but which differ solely in the spatial arrangement of the groups at the first carbon atom. In the case of some monosaccharides these two isomerides, which, as mentioned above, are called the α - and β -forms, are known. They differ in melting point, solubility, and particularly in optical behaviour. Thus, for α -glucose $[\alpha]_D$ is $+109.6^\circ$, and for β -glucose $+20.5^\circ$. If α -glucose is dissolved in water, the rotation gradually decreases to $+52.3^\circ$, and remains constant at that figure. If a solution of β -glucose is prepared its rotation increases until after a time it also remains at $+52.3^\circ$. This final value obviously corresponds to an equilibrium state between α - and β -sugar, which, in solution, are reversibly converted into one another:

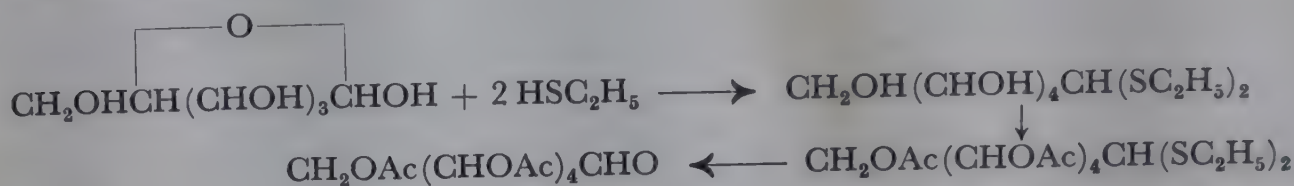


This phenomenon known as mutarotation is produced by the occurrence of this equilibrium.

It was Tollens who first proposed and laid the foundation of the cyclic hemiacetal, or oxide formula for the sugars. At present it is generally accepted. From the cyclic form (not from the carbonyl form) are derived the di- and poly-

saccharides, the glycosides, and probably almost all sugar derivatives in general. If occasionally the open-chain formula is still used — for didactic purposes, e.g. the formulation of the configurations of the sugars, it has certain advantages — it must be remembered that it does not represent accurately the actual linkages in the sugars.

The open-chain carbonyl form of glucose has been isolated in the form of the pentabenzoyl derivative (P. Brigl) and the pentaacetate (M. L. Wolfrom). These compounds are formed from D-glucose-diethylmercaptal pentabenzoylate and -acetate, respectively, by the careful elimination of the thioacetal radicals, e.g. with mercuric chloride:

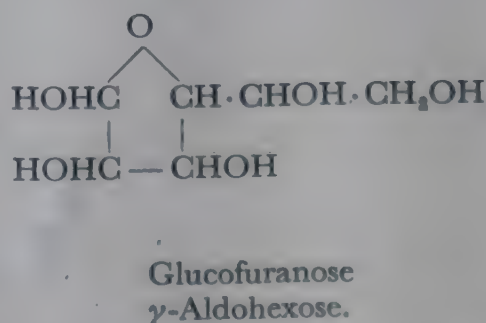
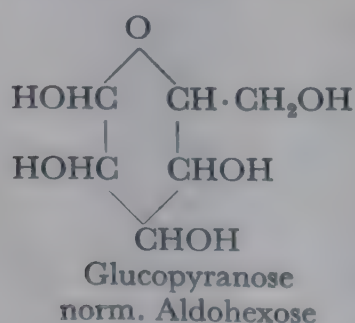


In the above cyclic formulæ, the "oxygen bridge" leads from the first to the fifth (i.e. the δ) carbon atom. Tollens originally put forward a γ -oxide ring in preference to the other possible ring systems without real proof, on the basis of the special ease with which γ -oxides (five-membered ring) are formed, and their great stability. More recent work, however (Helferich) has shown that cyclic hemiacetals are capable of existence which have six- and seven-membered rings. It is therefore possible that in different sugars the oxygen bridge occupies different positions, linking, for example, the carbon atoms 1 and 4, or 1 and 5, and that the same sugar may possess at one time, a β -, at another a γ -, and at a third time a δ -oxide ring. In the case of glucose and fructose isomerides have been found, which it is thought must be explained in this way.

Ordinary glucose appears to have a δ -oxide ring, at all events certainly in most of its derivatives, such as its acetyl compounds, methyl ethers, etc. (Haworth).

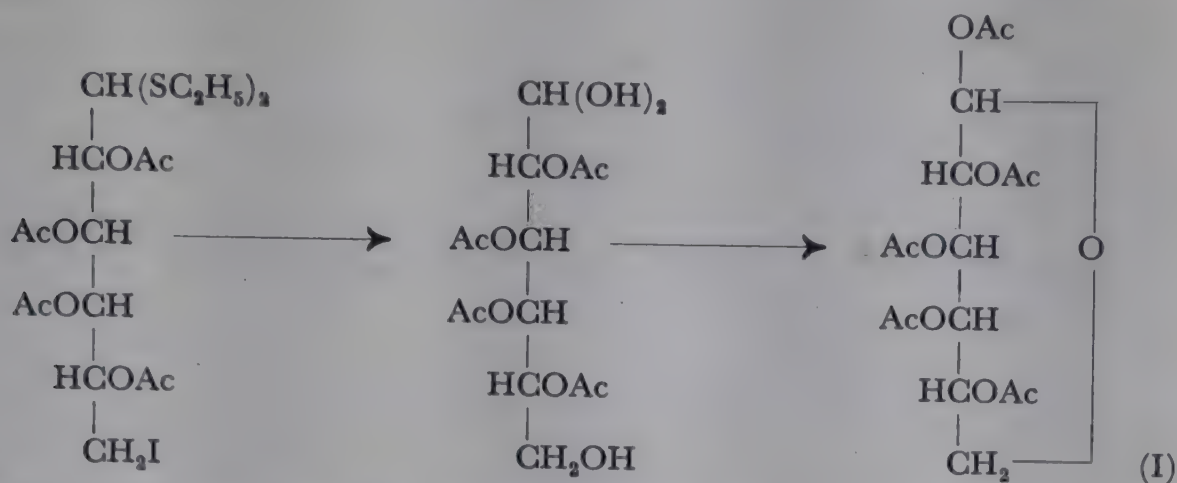
It is thus seen that the forms in which one and the same sugar molecule can exist are very numerous. Some phenomena connected with the normal and pathological degradation of carbohydrates in the organism, which at present are difficult so understand, may perhaps be related to these rearrangements.

W. N. Haworth proposed to derive the cyclic isomeric forms of the monosaccharides from the heterocyclic parent compounds *pyran* (see Ch. 43) and *furan* (see Ch. 59). The normal sugars can therefore be called *pyranoses* (derivatives of pyran), and the γ -sugars, derived from furan, *furanoses*. The two cyclic isomerides of glucose would thus be distinguished as glucopyranose and glucofuranose:



Micheel has been successful in preparing sugar derivatives synthetically, in which the oxygen-bridge in the cyclic hemiacetal form links the carbon atoms 1 and 6. The name *septanose* has been proposed for this seven-membered ring system. Pentaacetyl-galacto-

septanose (I) is formed from acetylated 6-iodo-galactose-diethylmercaptal by removing the iodine and the sulphur-containing groups by means of mercuric chloride and cadmium carbonate:



CHEMICAL PROPERTIES. The monosaccharides are powerful reducing agents. They precipitate silver from an ammoniacal solution of silver nitrate, and cuprous oxide from Fehling's solution. The latter reaction is used for the quantitative determination of sugars.

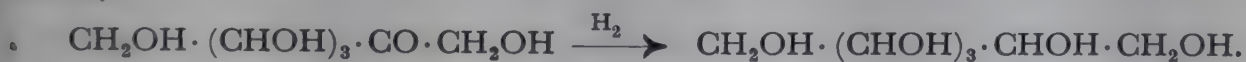
The aldoses give on mild oxidation (silver salts, bromine water) hydroxy-acids with the same number of carbon atoms (the so-called aldonic acids):



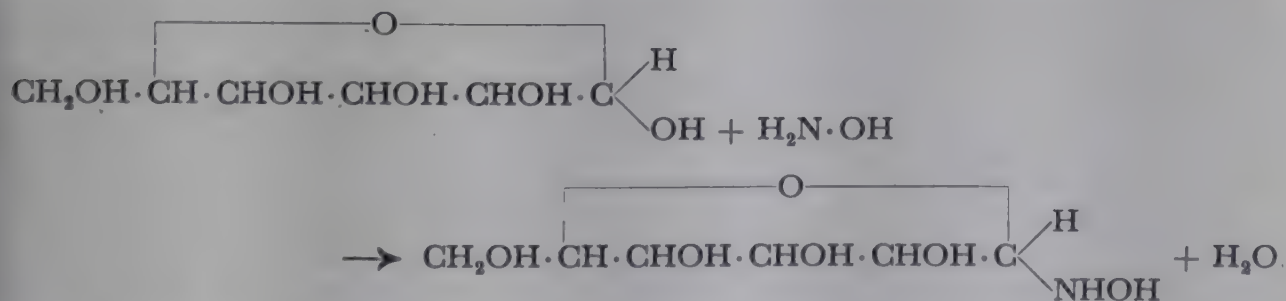
Concentrated nitric acid, on the other hand, oxidizes the sugar molecule at both ends and gives dicarboxylic acids:



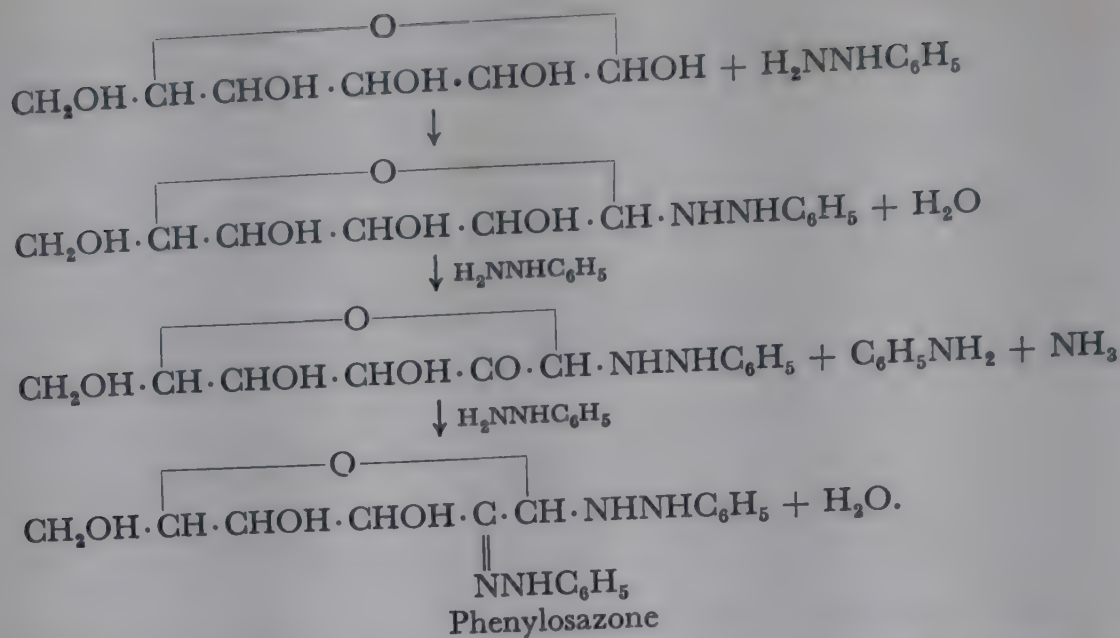
The reduction of aldoses and ketoses is usually carried out with sodium amalgam. Two atoms of hydrogen are taken up and polyhydric alcohols are formed:



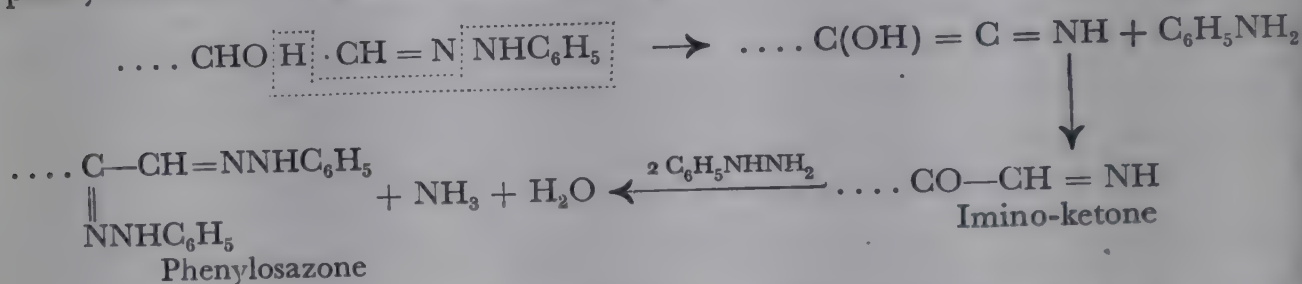
The behaviour of these substances towards hydroxylamine and hydrazine derivatives is very important. The former gives oximes with aldoses:



Phenylhydrazine, and similar aromatic hydrazine compounds (*p*-bromophenylhydrazine, *p*-nitrophenylhydrazine, benzylphenylhydrazine) react with aldoses and ketoses to give first hydrazones. Whilst it was formerly assumed that a second molecule of the hydrazine compound then oxidized the hydroxyl group adjacent to the original carbonyl group to CO, and that the new carbonyl compound reacted with a third molecule of phenylhydrazine to form an osazone,



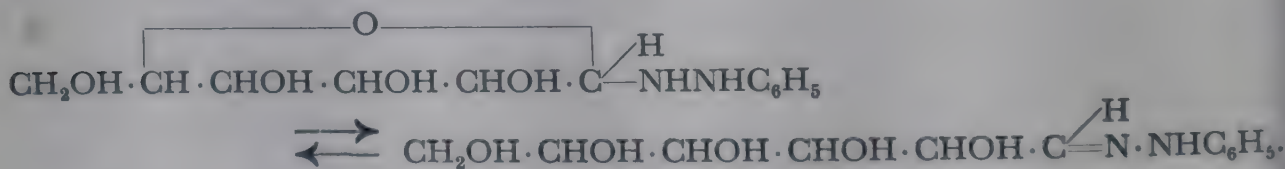
it is believed to-day that the transformation of the phenylhydrazone into the phenylosazone takes place as follows (cf. page 255):



According to this view, the simultaneous formation of aniline together with the osazone is thus due to an *intramolecular* reduction process.

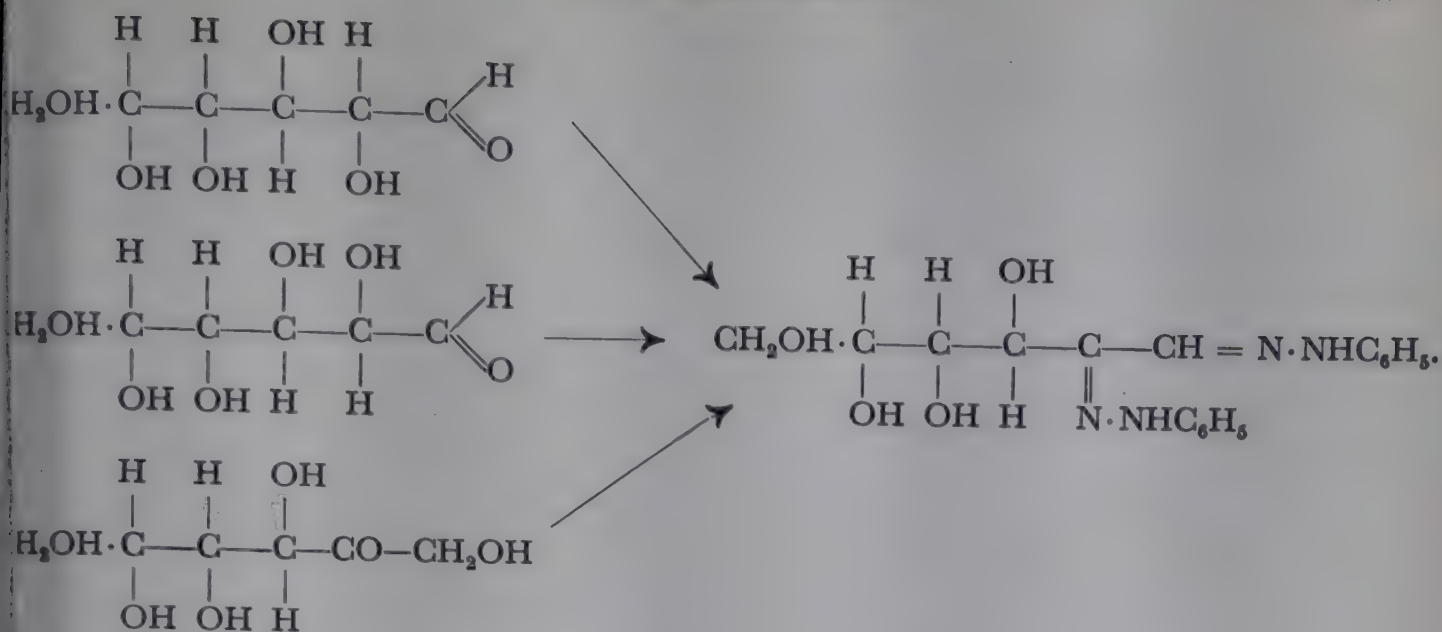
The osazones are yellow compounds, usually difficultly soluble in water, which crystallize excellently. On account of these convenient properties they are of great importance for the separation and characterization of the sugars.

Several phenylhydrazones are known in isomeric forms, and some of them show mutarotation, which is perhaps due to their consisting entirely or in part of molecules with the cycloacetal formula:



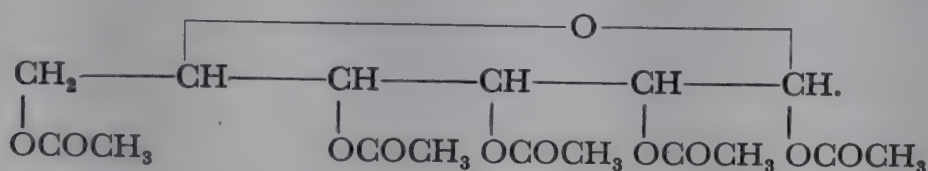
On the other hand Wolfrom and Christman are of the opinion that, for example, the hydrazones of galactose exist in the true hydrazone form, and not as cyclic galactose derivatives, since their acetates are identical with the compound obtained from 2:3:4:5:6-pentaacetyl-D-galactose and phenylhydrazine. Also Engel concludes from spectroscopic data that the osazones do not possess the cyclic hemiacetal structure, and ascribes their mutarotation to equilibria between the osazones and their products of hydrolysis.

The formation of osazones is associated with the disappearance of the asymmetry of the α -carbon atom. Therefore, two aldoses which differ only in the configurative arrangements of this carbon atom will give the same osazone. The latter is also obtained from the ketose which corresponds to these two aldoses as regards configuration:

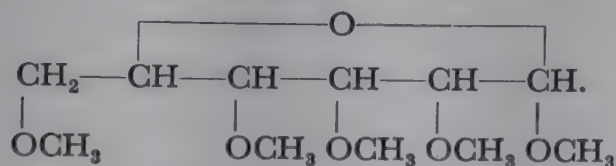


This phenomenon is of greatest use in the investigation of the configurational relationships of the sugars; for, if it is found that two aldoses give the same osazone, it follows that they differ only in the configuration at the α -carbon atom.

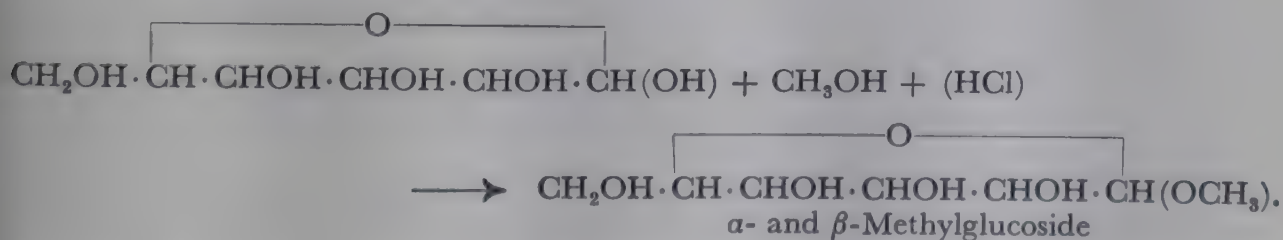
The hydroxyl groups of the sugars can be esterified and methylated. If glucose is heated with acetic anhydride and some zinc chloride, pentaacetylglucose is obtained:



On methylation (methyl iodide and silver oxide, or dimethyl sulphate and alkali) tetramethyl-methylglucoside¹ is obtained (Irvine, Haworth):



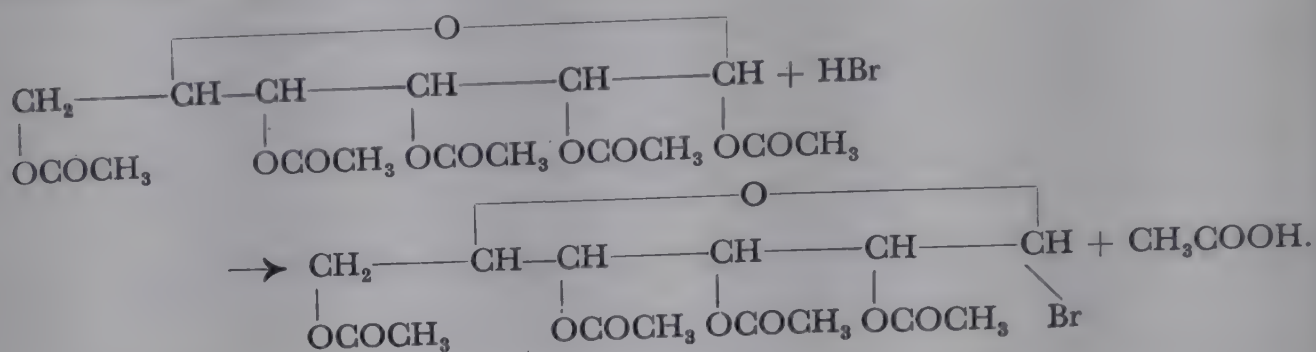
The acetal-hydroxyl group attached to the first carbon atom of glucose is particularly reactive. Even when the sugar is heated with methyl alcohol and some hydrogen chloride it is replaced by the methoxy-group. In this way the *methylglucosides* are produced, of which there are two, one derived from α -, the other from β -glucose:



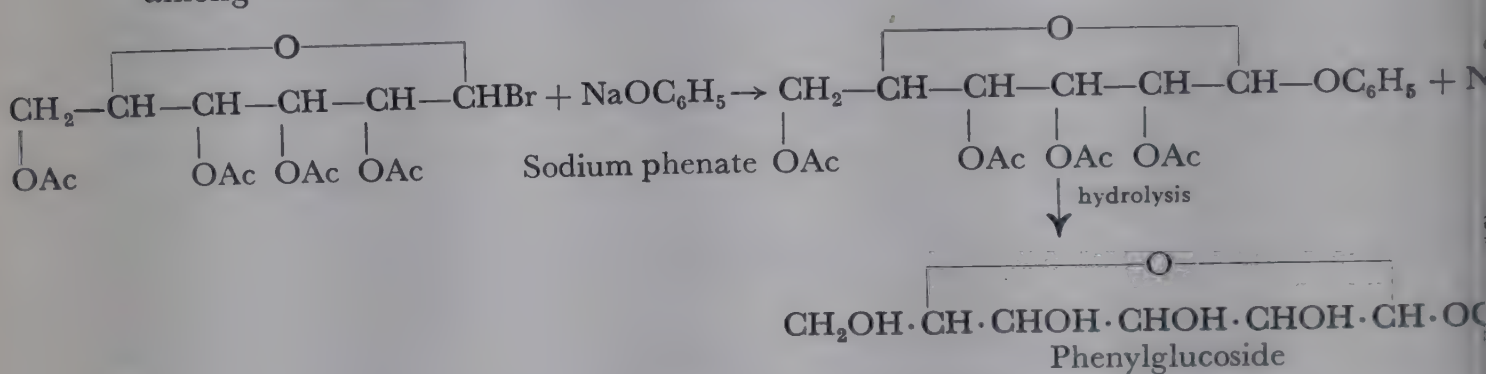
This glucoside synthesis, which was used by E. Fischer, is thus based on the

¹ For this derivative of glucose the δ -oxide structure has been proved.

preparation of acetals from simple aldehydes. A much more generally applicable method for the preparation of glucosides, however, uses tetraacetyl-1-chloroglucose, or tetraacetyl-1-bromoglucose. These important glucose derivatives are obtained by the action of acetyl chloride or acetyl bromide on glucose, or by the action of hydrogen bromide dissolved in glacial acetic acid on pentaacetylglucose:



The “acetobromoglucose” reacts smoothly with alcohols in the presence of silver carbonate giving acetylated alkylglucosides, and with sodium phenate to give phenylglucosides. The acetyl groups can later be eliminated by alkaline hydrolysis. This process has made it possible to synthesize dozens of different glycosides, among them numerous natural products:



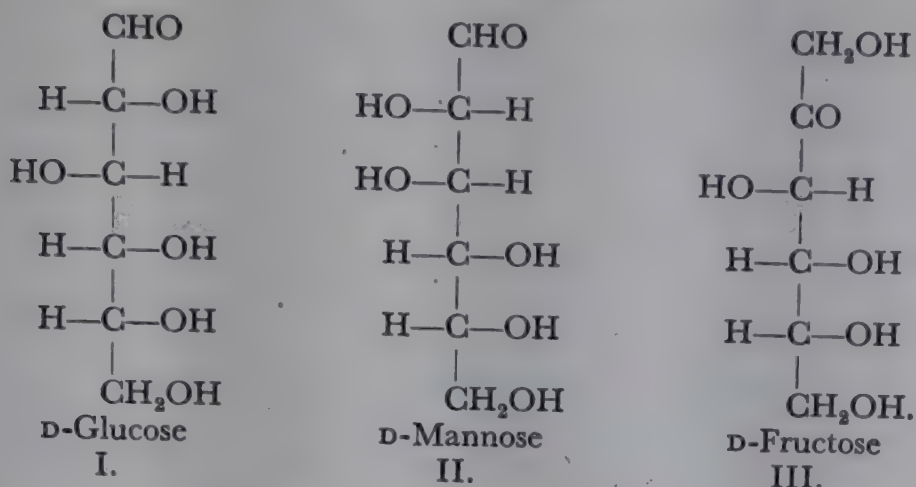
The behaviour of the glycosides towards enzymes is instructive. In most cases enzymes only hydrolyse those glycosides which are derived from natural sugars, yet their action on these is not general. It depends to a considerable degree on the configuration of the glycoside. There are those which will only attack α -glycosides. These are called α -glycosidases. They occur apparently quite abundantly. The most thoroughly investigated is that of yeast. On the other hand there are β -glycosidases which hydrolyse β -glycosides, the best known being *emulsin*, obtained from bitter almonds. Also the enzymic hydrolysis of glycosides is a reversible process. It is possible, using the same enzyme as will bring about hydrolysis, to effect syntheses. The method has been used by Bourquelot for the synthesis of many glycosides. The reversible process is completely analogous to that of esterification:



Finally, it may be mentioned here that the disaccharides, trisaccharides, etc. may be regarded as glycosides of the sugars. This will be returned to on p. 351.

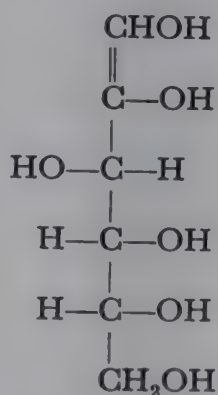
BEHAVIOUR OF SUGARS TOWARDS ALKALIS AND ACIDS. MUTUAL TRANSFORMATION OF ALDOSES. Whilst strong alkalis cause sugars to turn brown and decompose, dilute solutions of the hydroxides of the alkali and alkaline-earth metals, as well as

pyridine and quinoline produce peculiar rearrangements on warming. Thus, starting with glucose (I), an equilibrium mixture of mannose (II) and fructose (III) is obtained (Lobry de Bruyn and van Ekenstein):



The same equilibrium is set up if one of the last two sugars is acted upon by alkali. Glucose and mannose differ only in the configuration of the second α -carbon atom. Two such carbohydrates are said to be *epimeric*. One is formed from the other by α -inversion. Alkalis thus cause α -inversion of aldoses, and at the same time yield the ketose which gives the same osazone as the epimeric aldoses.

To explain these peculiar arrangements, which have also been used to synthesize new sugars, the assumption is made that these carbohydrates enolize when treated with alkali to the compound¹:

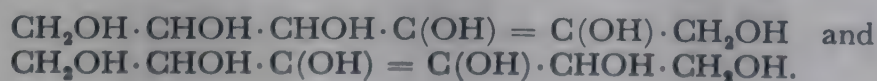


When this enediol form returns to the carbonyl form, it can obviously give rise to the two epimeric aldoses and the corresponding ketose.

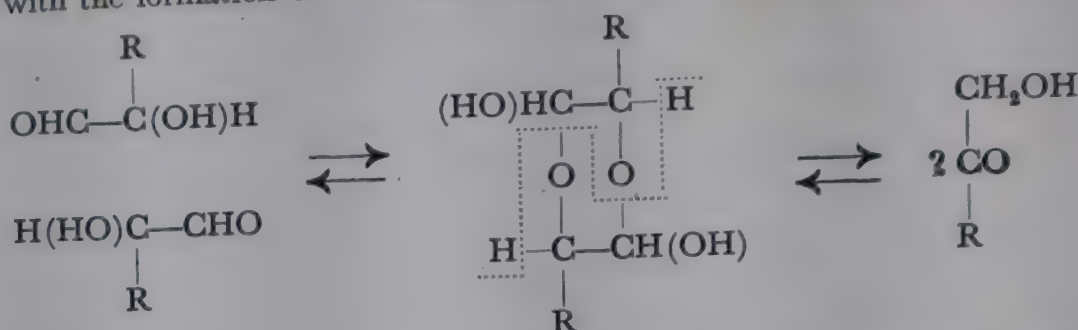
Transformations with methylated sugars make it very probable that the isomerization takes place through an enolic form of the above type. If, for example, 2:3:4-trimethylxylose is treated with calcium hydroxide, 2:3:4-trimethyllyxose is one of the products. A ketose is not formed in this case as the 2-position is methylated, thus preventing the enol form from becoming converted into a ketose.

Bonhoeffer and Fredenhagen observed that in heavy water it is possible to convert glucose into fructose without any deuterium entering the fructose molecule, if the reaction is carried out at low temperatures (not a higher ones) and if the alkalinity is kept low. This gives rise to their assumption that under these special conditions the reaction takes place

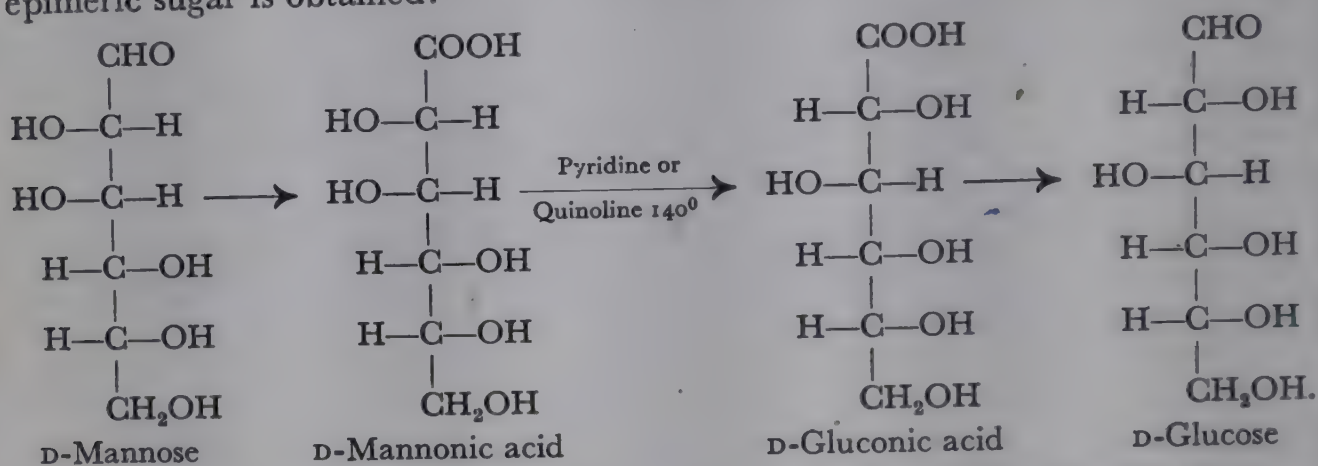
¹ Perhaps in addition other enediol forms are produced, such as:



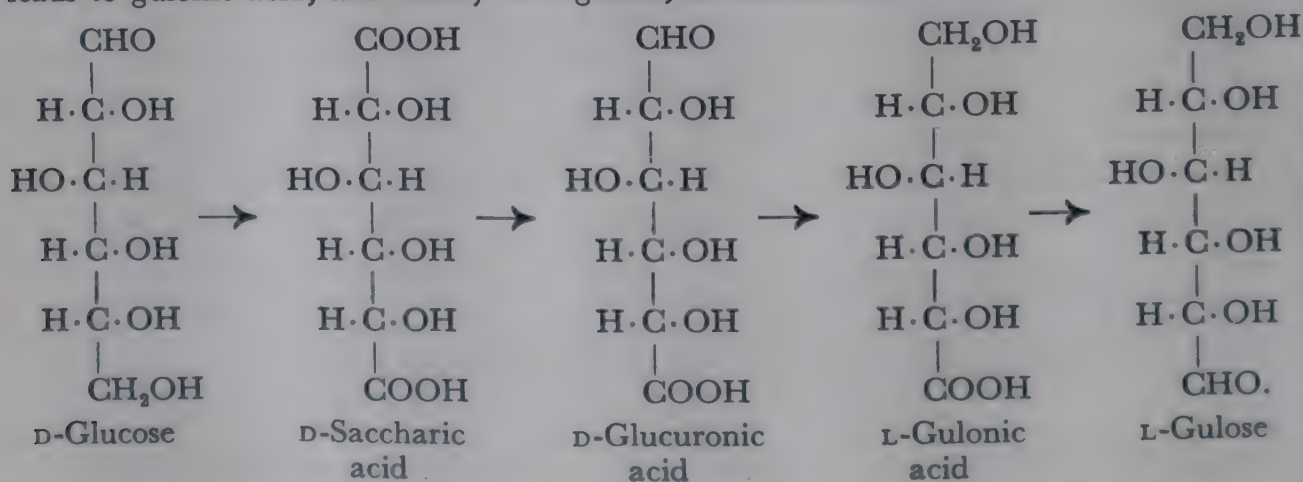
according to some mechanism other than the one discussed above. They assume that, as in the case of the Cannizzaro reaction with glyoxal (p. 257), two molecules of glucose first combine with the formation of a dioxane ring, fission of this ring then yielding fructose:



There is, in addition, another way of converting a sugar into the epimeric form. The aldose is oxidized to the monocarboxylic acid, and the latter is heated with quinoline or pyridine to 140°, or with ammonia under pressure. This causes partial α -inversion. If the lactone of the new aldonic acid is now reduced, the epimeric sugar is obtained:

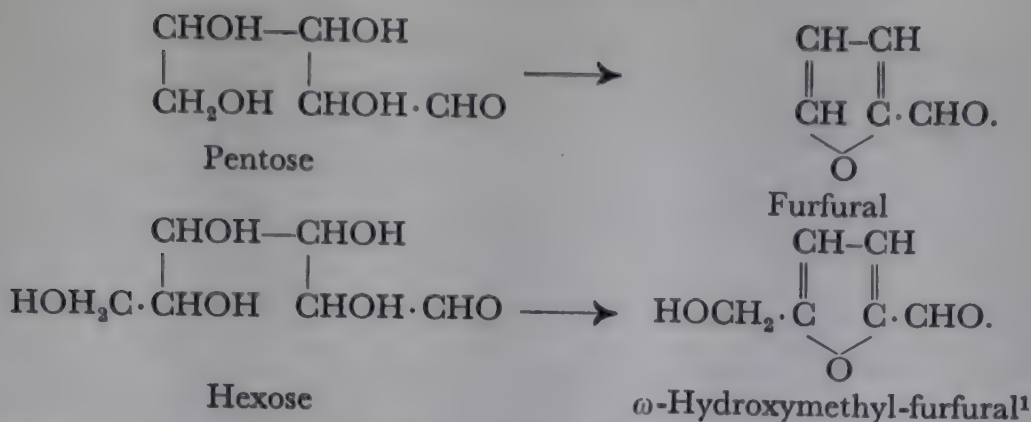


Occasionally another method has been used to discover the configurational relationships between aldoses, by which the aldehyde and primary alcohol groups of an aldose are exchanged. If D-glucose is oxidized to the dicarboxylic acid (D-saccharic acid), and the lactone of this is reduced, an aldehydic acid, glucuronic acid, is formed. Further reduction leads to gulonic acid, and finally to L-gulose, an aldohexose:



Zinc hydroxide ammonia has a profound degradative action on hexoses. Windaus has isolated the heterocyclic compound 4-methylimidazole (see Ch. 60) from the solution, which is presumably formed from methylglyoxal and formaldehyde produced by the decomposition of glucose.

Mineral acids when heated with carbohydrates remove water. *Furfural* is formed from pentoses, and ω -hydroxymethyl-furfural from hexoses:



(These reactions presumably pass through intermediate stages such as $\text{HOCH}_2\cdot\text{CHOH}\cdot\text{CHOH}\cdot\text{CH}=\text{C}(\text{OH})\text{CHO}$ and $\text{HOCH}_2\cdot\text{CH}\cdot\text{CHOH}\cdot\text{CH}=\text{C}\cdot\text{CHO}$).

The furfural which is fairly stable towards acids, distils off with steam, and can thus be separated. Its formation gives rise to various colour reactions which are used as tests for pentoses. If a pentose is warmed with some phloroglucinol and hydrochloric acid a deep violet-red coloration is formed; with orcinol, some ferric chloride and hydrochloric acid, a green coloration is produced. A quantitative determination of pentoses depends on distilling off the furfural produced by the action of an acid, combining it with phloroglucinol to give an insoluble condensation product, and weighing this.

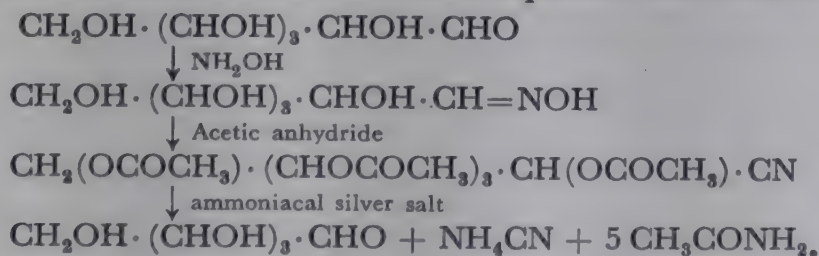
ω -Hydroxymethyl-furfural is further converted by the action of hot acids into lævulinic acid (see p. 271), which is therefore found as the principal product of the action of mineral acids on hexoses.

DEGRADATION OF MONOSACCHARIDES. Two methods are available for converting an aldose to the next lower member, e.g. for converting a hexose into a pentose:

(a) Ruff degradation: The aldose is oxidized with hydrogen peroxide in the presence of basic ferric acetate or mercuric oxide. α -Ketonic acids are probably formed as intermediate products. The aldohexonic acid, preferably in the form of its calcium salt, may, of course, also be oxidized:



(b) Wohl degradation. By heating the aldose oxime with acetic anhydride the acetyl derivative of the corresponding aldonic acid nitrile is produced. Ammoniacal silver salt removes the acetyl radicals and hydrocyanic acid, so that an aldose is produced which is one carbon atom poorer than that of which the oxime was used:

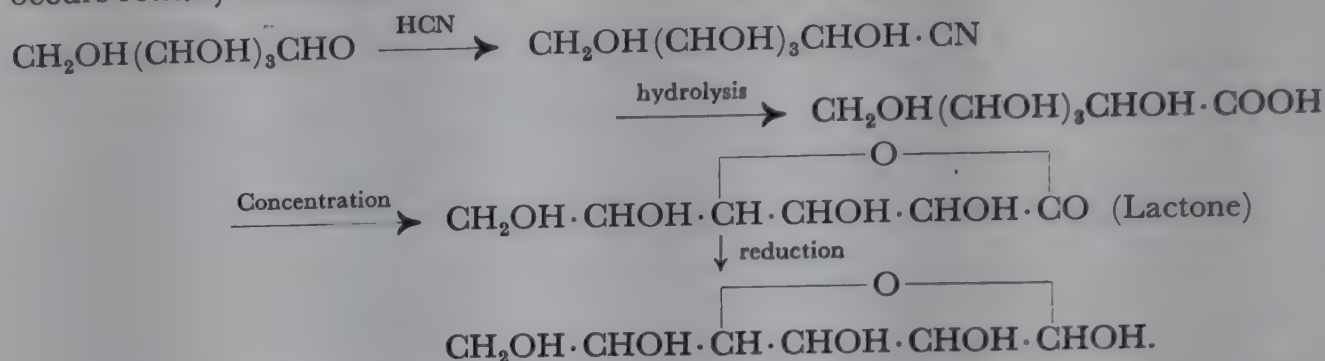


The fermentations of the monosaccharides brought about by moulds and bacteria also rank as degradation reactions. They always lead to relatively low stages of degradation. The most important of them have already been dealt with, viz. the alcoholic fermentation (see p. 89), lactic acid fermentation (see p. 262), citric acid fermentation (see p. 320), and the butyric acid fermentation (see p. 202).

¹ The terminal carbon atoms of a compound are often given the symbol ω , a terminology due to Baeyer, e.g. $\text{CH}_2\text{OH}(\text{CH}_2)_4\text{COOH} = \omega$ -hydroxycaproic acid.

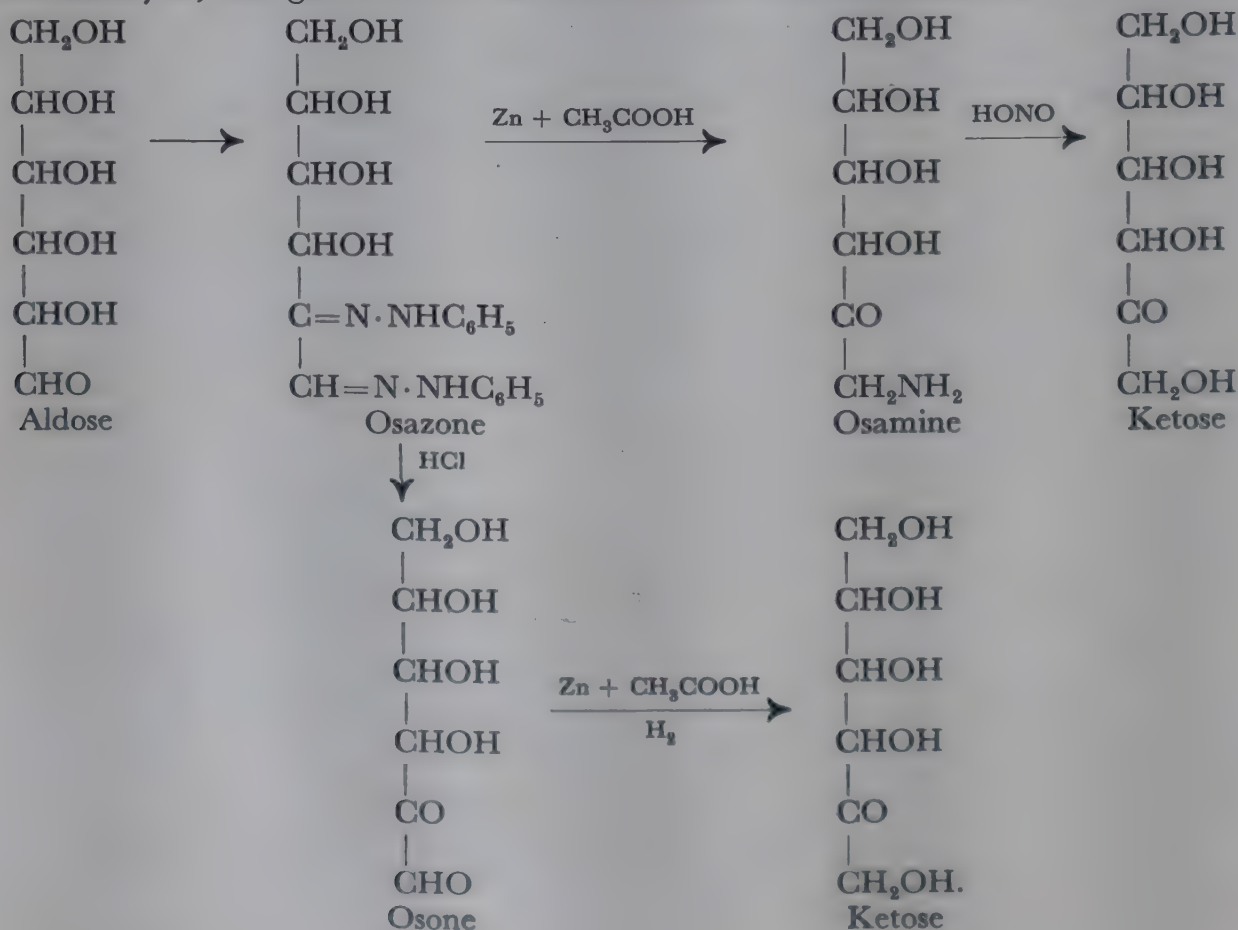
A bacterial fermentation which occasionally occurs in beer and wine converts glucose into a slimy mass. In addition, some mannitol is also formed.

SYNTHESIS OF MONOSACCHARIDES. A method worked out by Kiliani and E. Fischer makes it possible to pass from a tetrose to a pentose, from this to a hexose, etc. Hydrocyanic acid is added to the aldose, the cyanhydrin produced is hydrolysed to the aldonic acid, and the lactone of the latter is reduced. Whilst the reduction of an aldonic acid itself to an aldehyde is not possible, the reaction occurs readily with the lactone when sodium amalgam and water are added:

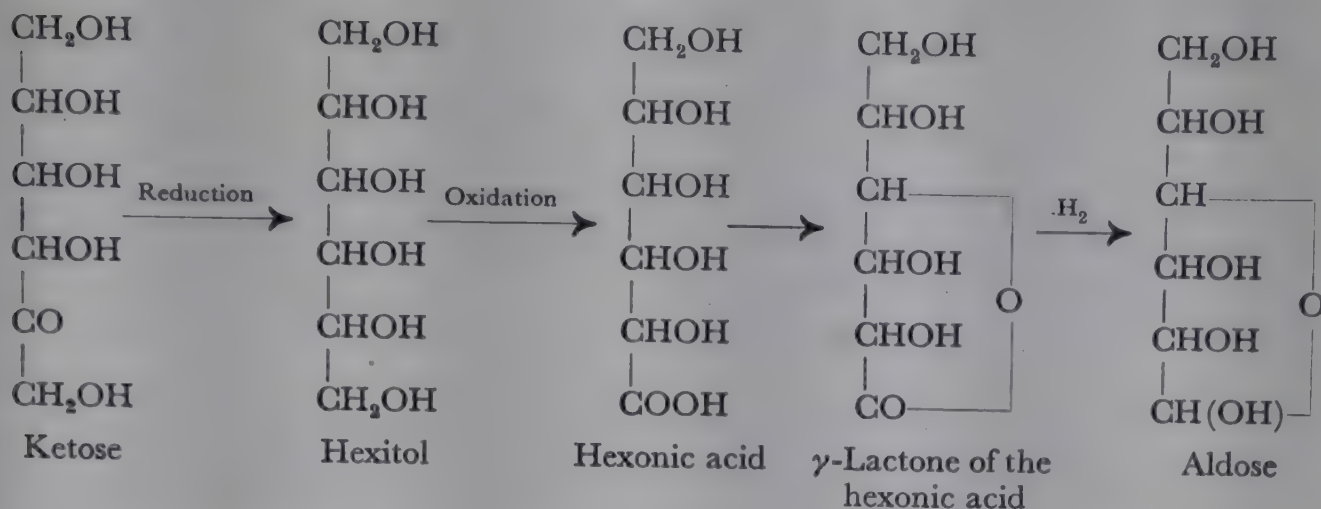


On transition from a pentose to a hexose a new asymmetric carbon atom makes its appearance, which makes possible the formation of two epimeric sugars. Actually the two isomerides are frequently formed together. Conversely, the degradation of two epimeric monosaccharides gives the same lower sugar, since in this case an asymmetric carbon atom disappears.

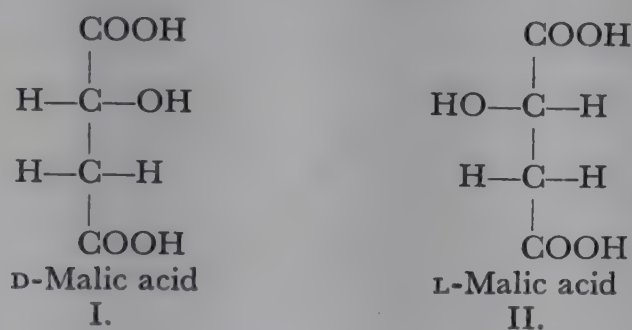
INTERCONVERSION OF ALDOSES AND KETOSES. The conversion of an *aldose* into a *ketose* can be brought about through the osazone. This is reduced by zinc dust and acetic acid to an *osamine*, an amino-derivative of a ketose, which gives the ketose itself on treatment with nitrous acid. In another method, the osazone is converted into an *osone* by means of fuming hydrochloric acid. This is a keto-aldehyde, and gives the ketose when treated with zinc dust and acetic acid:



The reverse process, the transformation of a *ketose into an aldose* can be carried out by first reducing the ketose to the corresponding polyhydric alcohol, oxidizing this to the aldonic acid, and then adding on hydrogen to the lactone of this acid:



Configuration of the sugars and their immediate derivatives. For the derivation of the configurational formulæ of the sugars, malic acid will be chosen as the starting point, and D-malic acid will be assigned formula I, and L-malic acid, formula II:

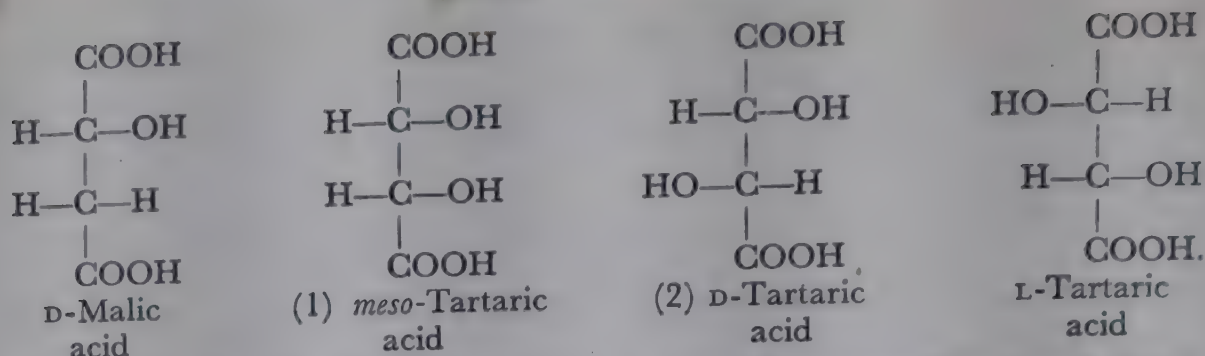


This choice is quite arbitrary. Since however, for a long time, it had not been possible to determine the absolute configuration of a pair of antipodes, the choice had to be made for any one pair of enantiomorphs. This forms the basis of all further derivations which connect in a strictly logical manner the space formulæ of other compounds with those of the primary substance.

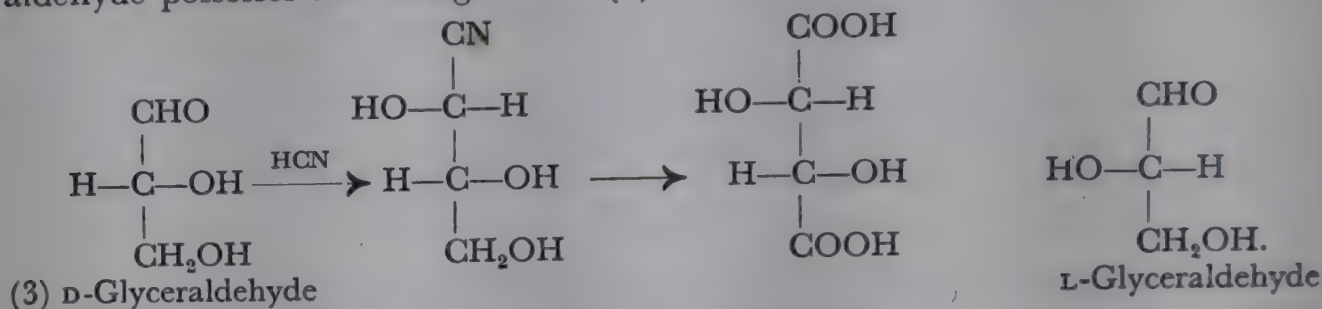
Recently Werner Kuhn has endeavoured to derive the "*absolute configurations*" of some simple optically active compounds, such as L(+)-lactic acid, on theoretical grounds. He obtains the same stereochemical formulæ as those obtained for the optical isomerides on the basis of the arbitrary choice made above. (For the stereo-formula of L(+)-lactic acid see p. 303, and for that of malic acid, see above.)

All sugars which are derived, as far as configuration is concerned, from D-malic acid or D-glyceraldehyde, are called D-sugars, and their antipodes L-sugars.

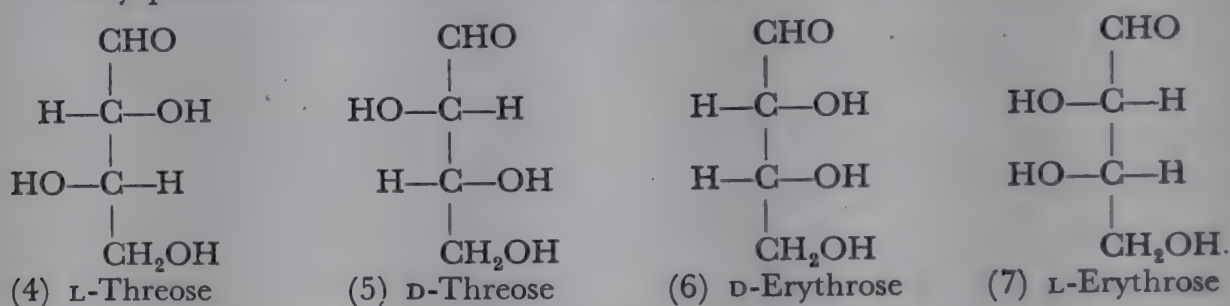
The spatial structure of the *tartaric acids* can be derived from that of the malic acids, since D-tartaric acid can be reduced to D-malic acid. Thus only the configurations (1) and (2) are available for D-tartaric acid; of these (1) is out of the question, as it is symmetrical. D-Tartaric acid must therefore have the structure (2). (1) is meso-tartaric acid.



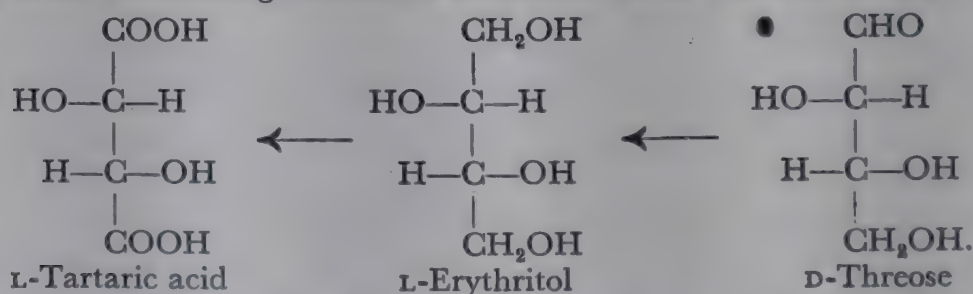
The simplest optically active aldoses are the *glyceraldehydes*; of these the D-form gives rise to L-tartaric acid by the cyanhydrin synthesis. Hence, D-glyceraldehyde possesses the configuration (3):



Theory predicts the existence of four stereoisomeric ALDOTETROSES:

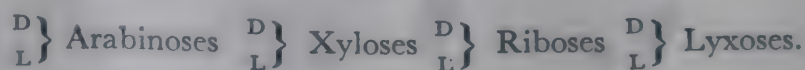


All four sugars are known. D-Threose yields on reduction L-erythritol (dextro-rotatory in aqueous solution), of which the formula is given by its oxidation to L-tartaric acid. The configuration of D-threose must therefore be (5):



The configurations of the two erythroses is best derived from those of the pentoses. We shall see immediately that the degradation of L-arabinose to L-erythrose proves that the latter has the formula (7), and D-erythrose formula (6).

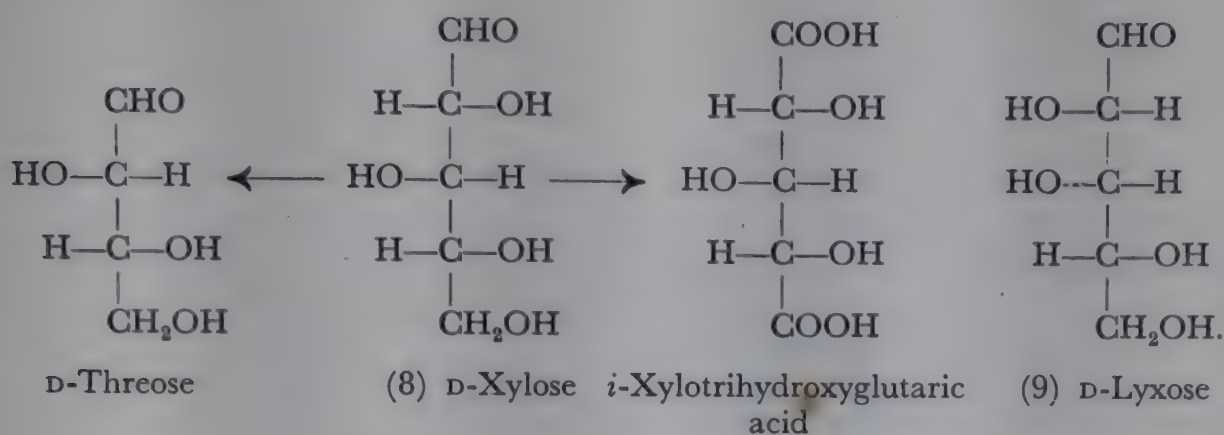
PENTOSEs. The three asymmetric carbon atoms of the pentoses demand the existence of four pairs of antipodes:



All are known.

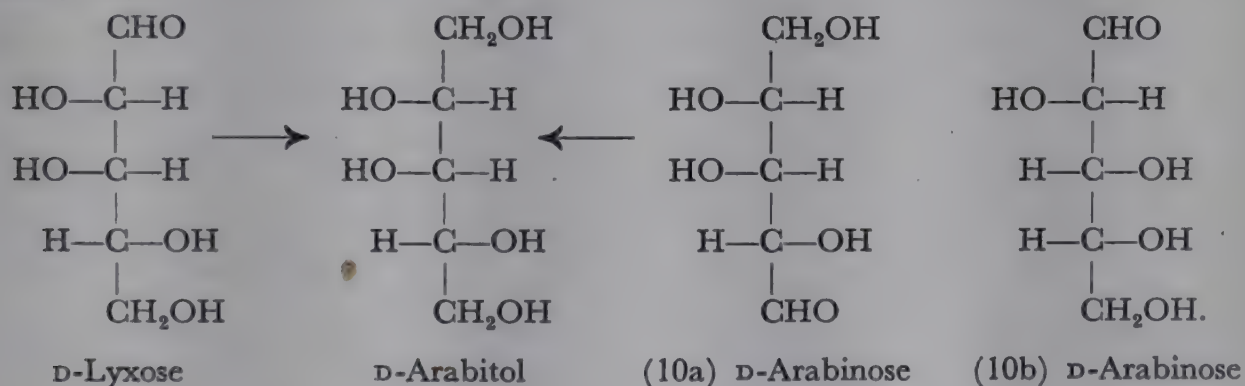
D-Xylose gives on degradation D-threose, and on oxidation the internally compensated inactive *xylotrihydroxyglutaric acid*. Hence, D-xylose must have formula (8). The epimeric configuration (9) which also fits the conversion of D-xylose

into D-threose, is excluded, since a compound with this structure would furnish an optically active trihydroxyglutaric acid:

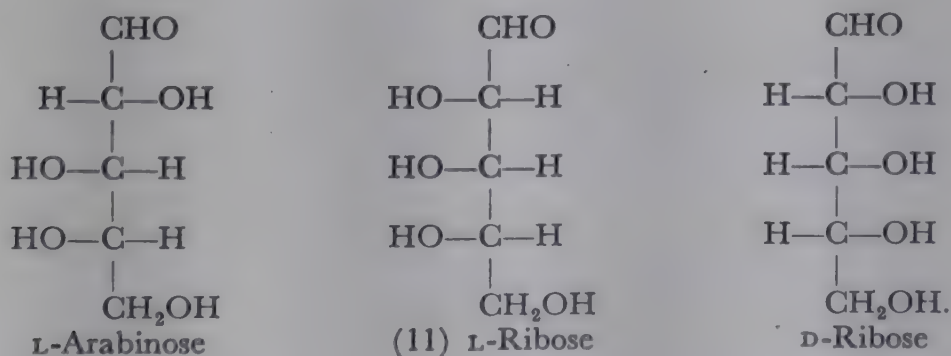


D-Lyxose has the formula (9), since it gives the same osazone as D-xylose, and is therefore epimeric with it.

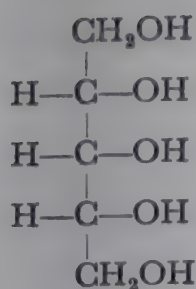
The formula of D-arabinose is arrived at as follows: this sugar gives on reduction, the same alcohol as D-lyxose, viz. D-arabitol. The configuration of this follows from that derived for D-lyxose. If two aldoses give the same alcohol on reduction, or the same dicarboxylic acid on oxidation, their formulæ must differ in that the positions of the primary alcohol group and the aldehyde group are interchanged; for both these groupings become identical on oxidation or reduction. Hence D-arabinose must have the form (10a), or rotated through 180°, form (10b):



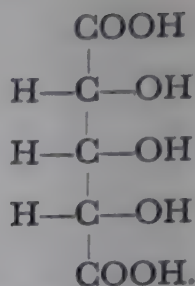
L-Ribose (11) and L-arabinose yield the same osazone. Their formulæ are therefore:



The two active riboses give, on reduction, the inactive, non-resolvable alcohol *adonitol*, and on oxidation the internally compensated *ribotrihydroxyglutaric acid*:

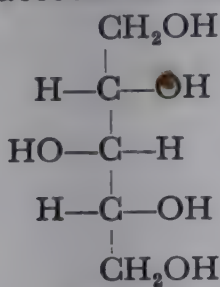


Adonitol

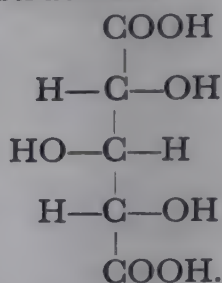


Ribotrihydroxyglutaric acid

The pentahydric alcohol *xylitol* and *xylotrihydroxyglutaric acid* stand in the same relationship to the two optically active xyloses. These two substances are not resolvable on account of their symmetrical structure:

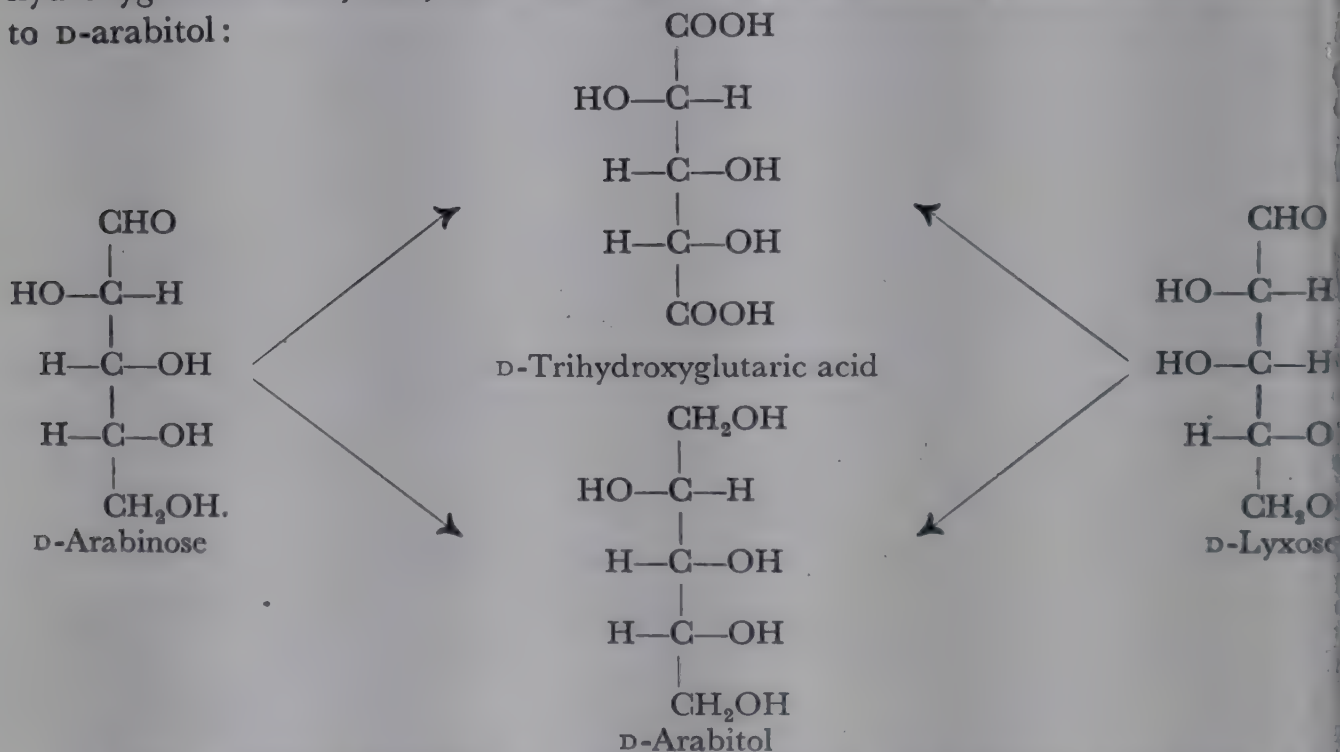


Xylitol

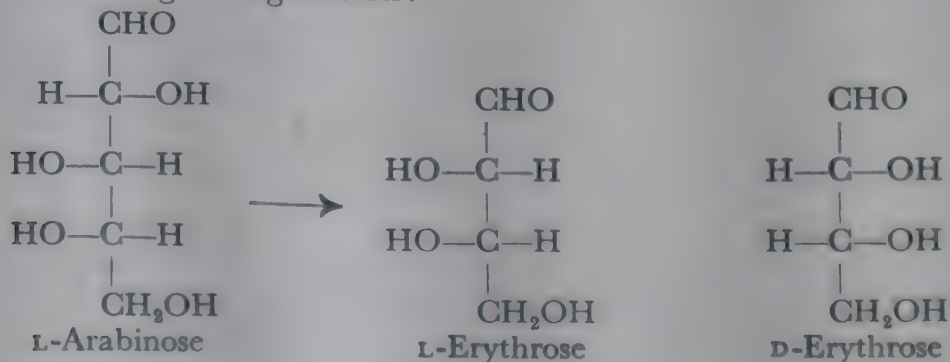


Xylotrihydroxyglutaric acid

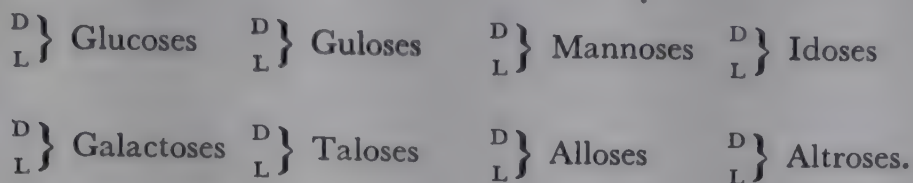
D-Arabinose and D-lyxose, on the one hand, can be oxidized to the same D-trihydroxyglutaric acid, and, on the other hand, as mentioned above, are reduced to D-arabitol:



From the steric structure of L-arabinose those of the *erythroses* can now be obtained, since L-erythrose is formed by the degradation of L-arabinose, and therefore has the following configuration:

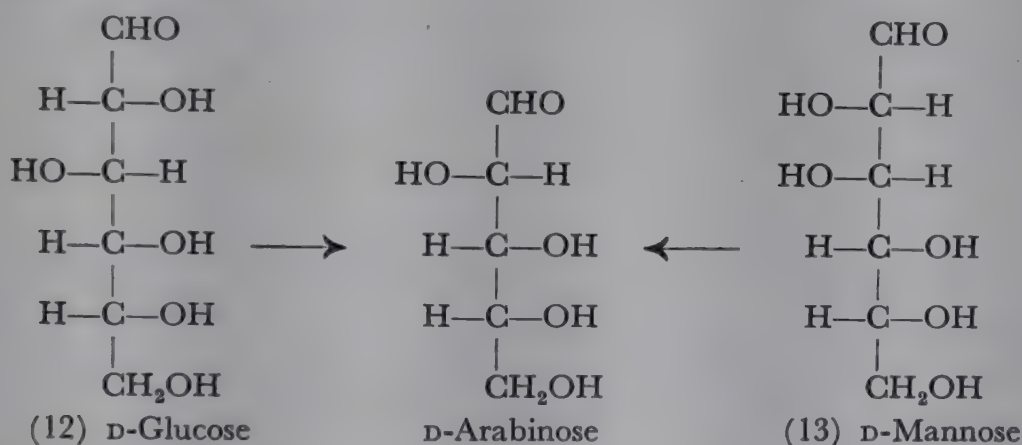


HEXOSES. The four asymmetric carbon atoms of the hexoses require that 16 stereoisomers should exist. These have all been obtained synthetically. Their names are:

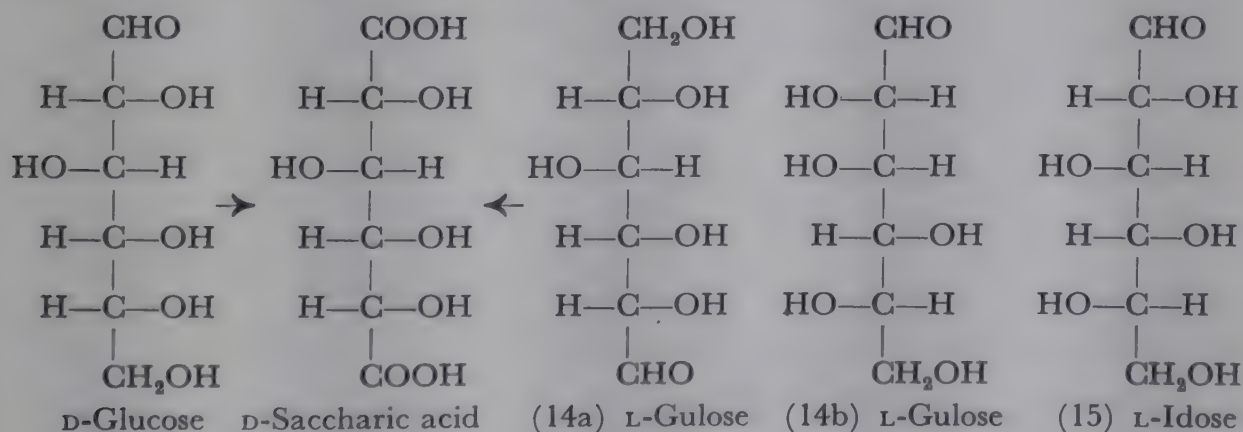


The derivation of the configurations of the aldohexoses is based on the following considerations:

Degradation of *D-glucose* leads to *D-arabinose*. Two formulæ (12) and (13) are possible for *D-glucose* based on this fact. The second of these can be excluded on the following grounds: *D-glucose* and a second sugar, *L-gulose*, give on oxidation the same dicarboxylic acid (*D-saccharic acid*). If *D-glucose* had the formula (13), that of *L-gulose* would be obtained from it by exchanging the aldehyde and primary alcohol groups. This, however, as the diagram shows, would lead to a molecule which is identical with (13), since on rotation through 180° the two formulæ can be superimposed. Since identical formulæ can obviously not be assigned to two different sugars (*D-glucose* and *L-gulose*), (13) cannot be the formula of *D-glucose*. Its formula is therefore (12):

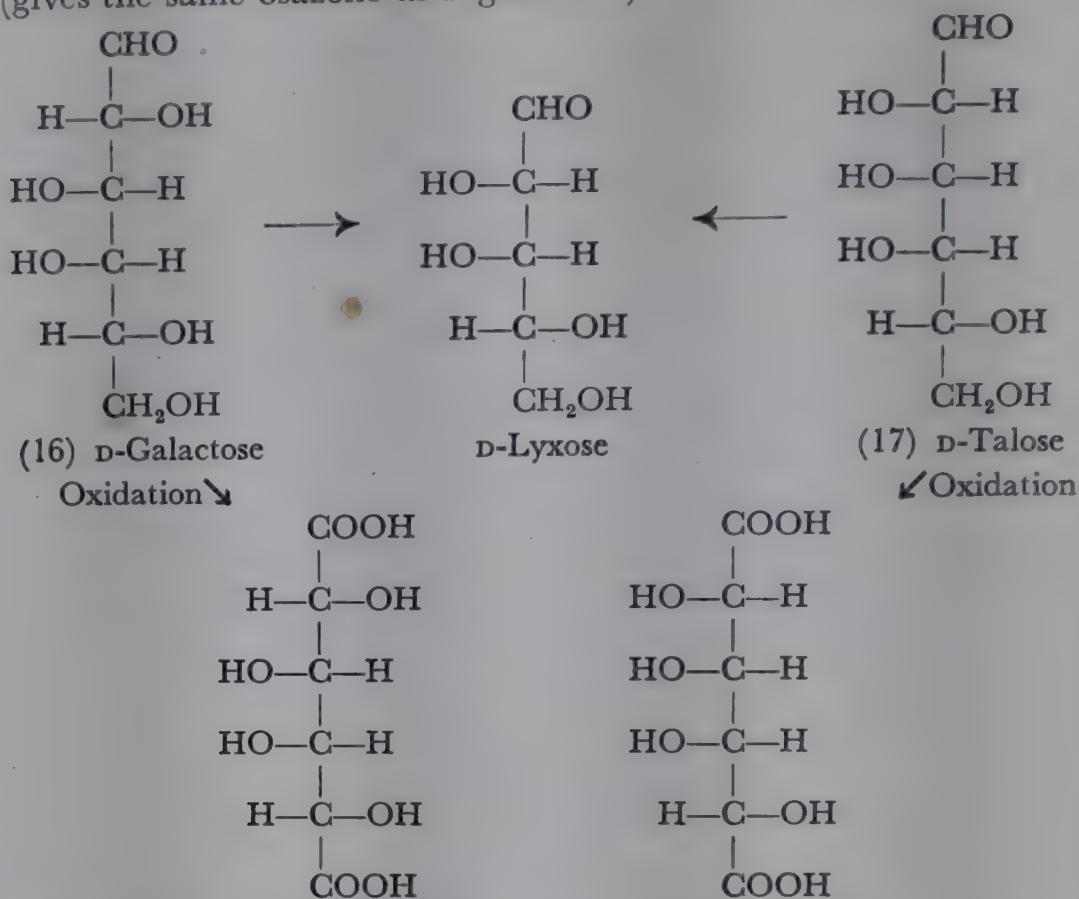


The sugar (13) which is epimeric with *D-glucose* is *D-mannose*, as is indicated by the identity of their osazones. That sugar which gives on oxidation the same dicarboxylic acid as *D-glucose*, *L-gulose*, must have the formula (14a), which, when rotated through 180° is identical with formula (14b):



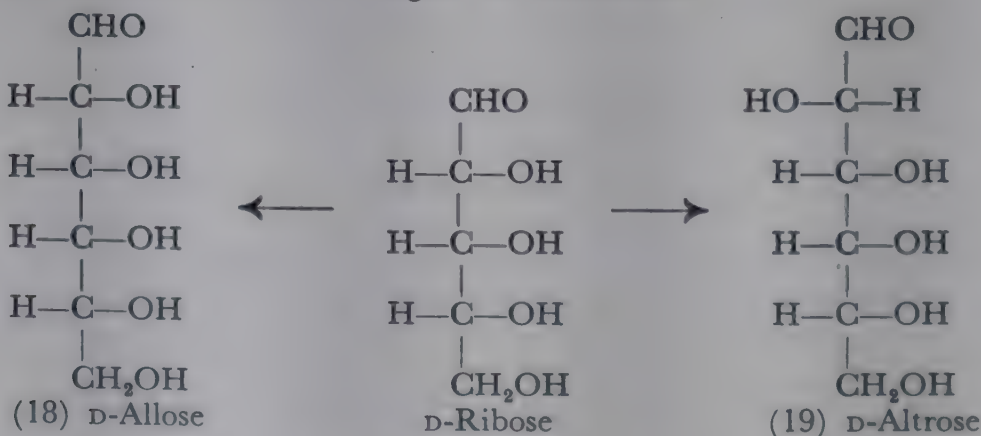
L-Gulose and *L-idose* are epimeric (identical osazones). Hence *L-idose* has the formula (15).

D-Galactose gives *D-lyxose* on degradation. The two possible formulæ for it are therefore (16) and (17). To assign the correct formula it must be noted that oxidation of *D-galactose* gives the *internally compensated mucic acid*. This shows that *D-galactose* has the configuration (16). The formula (17) is that of the epimeric *D-talose* (gives the same osazone as *D-galactose*):

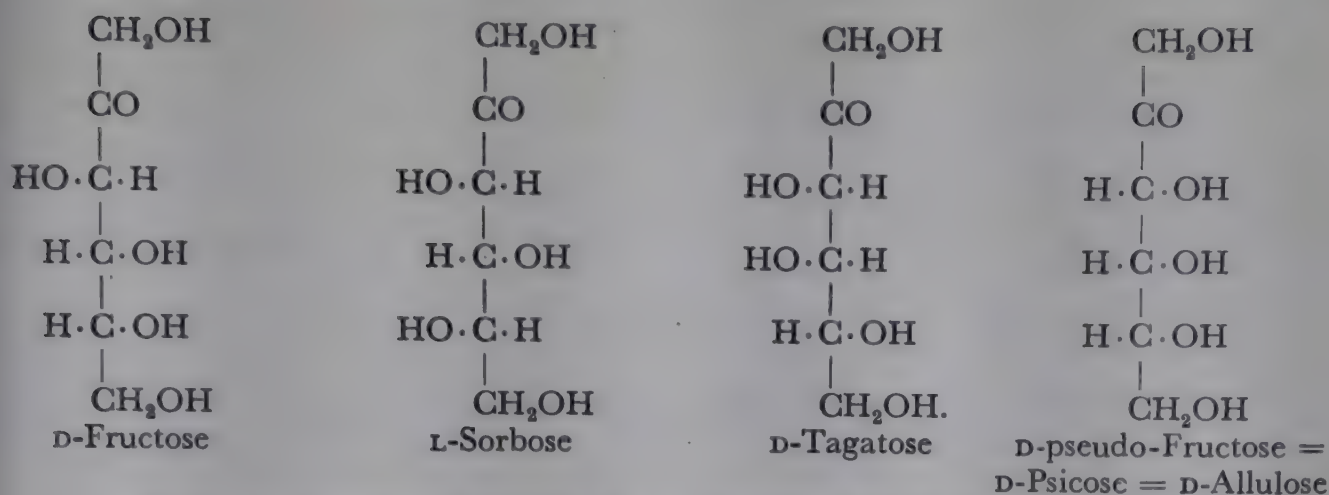


Mucic acid (inactive, non-resolvable) *D-Talomucic acid*

The two epimeric hexoses *D-allose* and *D-altrose* are formed by synthesis from *D-ribose*. The two formulæ (18) and (19) must therefore have been correctly assigned to them. Since *D-altrose* gives an *optically active* tetrahydroxyadipic acid (*D-talomucic acid*), formula (19) must be that of *D-altrose* and (18) that of *D-allose*. The osazones of the two sugars are identical:



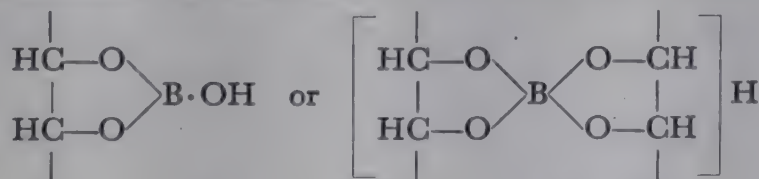
KETOSES The configurational formulæ of *D-fructose*, *L-sorbose*, and *D-tagatose* are obtained at once from their relationships with the aldohexoses: *D-Fructose* gives the same osazone as *D-glucose* and *D-mannose*, *L-sorbose* the same as *L-gulose* and *L-idose*, and the osazone of *D-tagatose* is identical with that of *D-galactose* and *D-talose*, whilst both *D-allose* and *D-psicose* also form identical osazones. The formulæ of these ketoses are therefore:



Finally, the polyhydric alcohols and dicarboxylic acids connected with the aldoses will be summarized:

Hexoses	Osazones	Alcohols	Dicarboxylic acids
D-Glucose	m.p. 205°	Sorbitol m.p. 110–111°	Saccharic acid m.p. 125–126°, m.p. of the lactone, 130–132°.
L-Gulose	m.p. 156°	Sorbitol	Saccharic acid.
D-Mannose	m.p. 205°	Mannitol m.p. 165°	Mannosaccharic acid, m.p. of the lactone, 180– 190°.
L-Idose	m.p. 156°	Iditol m.p. 73.5°	Idosaccharic acid, a syrup.
D-Galactose	m.p. 188°	Dulcitol m.p. 188.5°	Mucic acid, m.p. about 213° (other authors, 255°).
D-Talose	m.p. 188°	Talitol m.p. 86°	Talomucic acid, m.p. about 158°.
D-Altrose	m.p. 183–185°	Talitol	Talomucic acid.
D-Allose	m.p. 183–185°	—	Allomucic acid, m.p. 198–200°

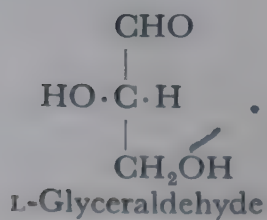
In the derivation of the configurations of the monosaccharides, no attention has been paid to further cases of stereoisomerism, which appear to be possible if the sugars are represented by the cyclic hemiacetal formulæ instead of the open-chain formulæ. Some monosaccharides are known to exist in α - and β -forms, as mentioned above, these forms differing in the positions of the substituents at the first carbon atom. The two glucoses are thought to have the formulæ given below. The work of Böeseken in particular supports this. He showed that, as a rule, only those polyhydric alcohols which have two neighbouring hydroxyl groups in the *cis*-position (and thus on the same side of a plane through the carbon atoms) combine with boric acid to form boric esters of the type:

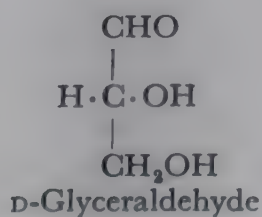
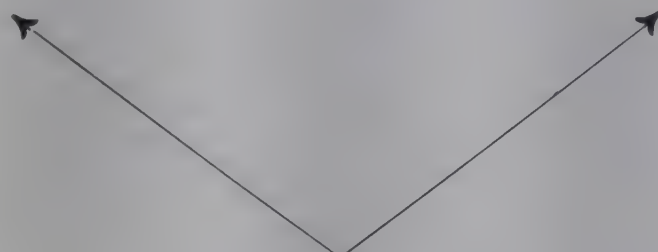
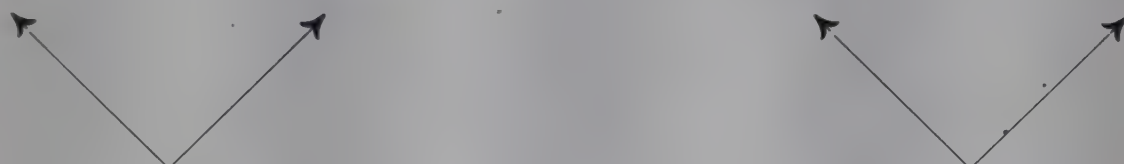
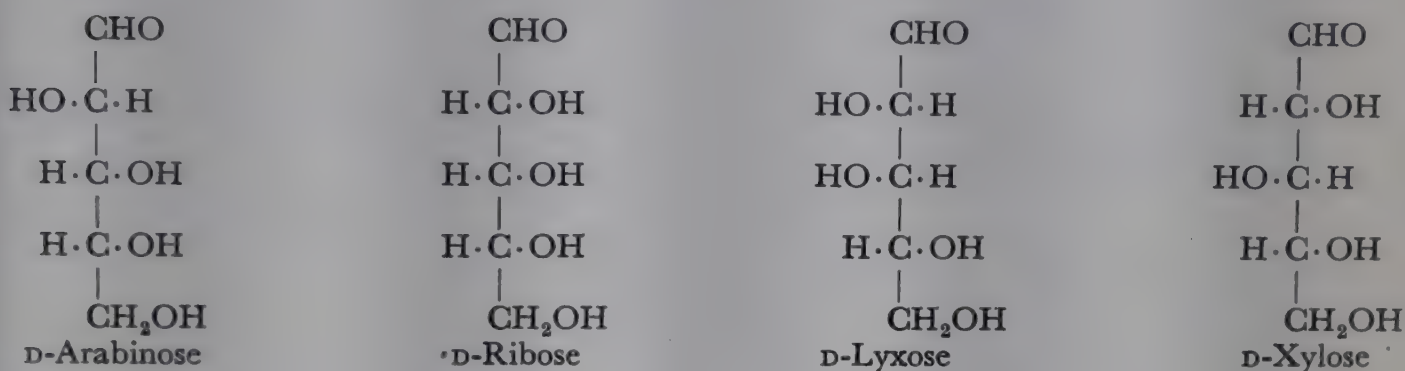
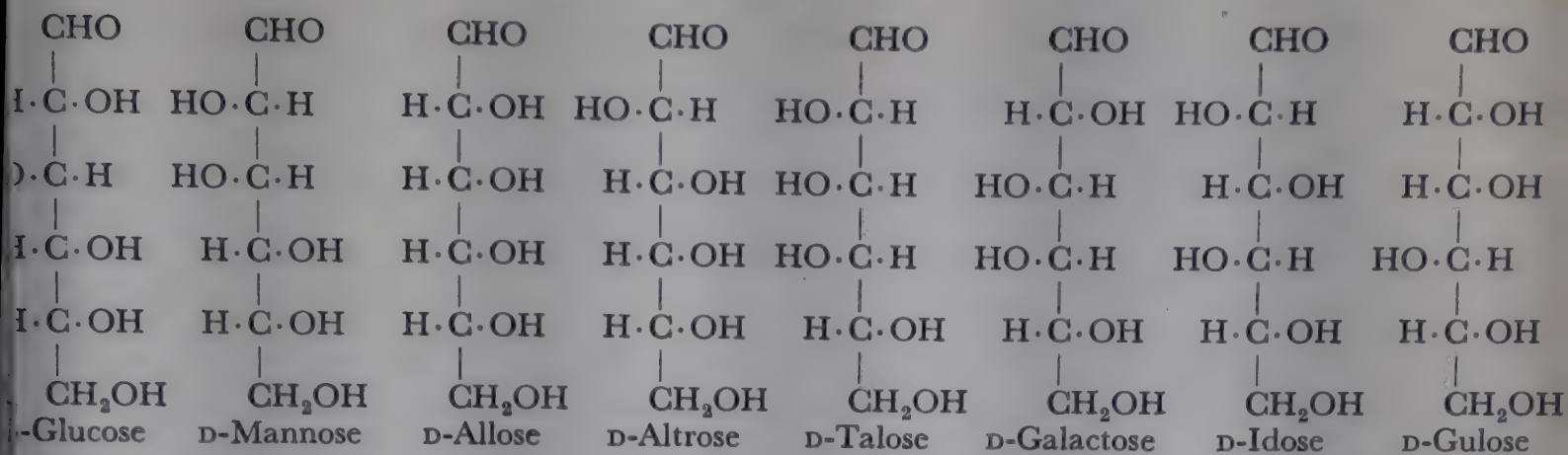


and increase the conductivity of a boric acid solution (cf. p. 114). It is therefore possible to draw conclusions concerning the configuration of a polyhydric alcohol from its effect on the conductivity of a solution of boric acid.

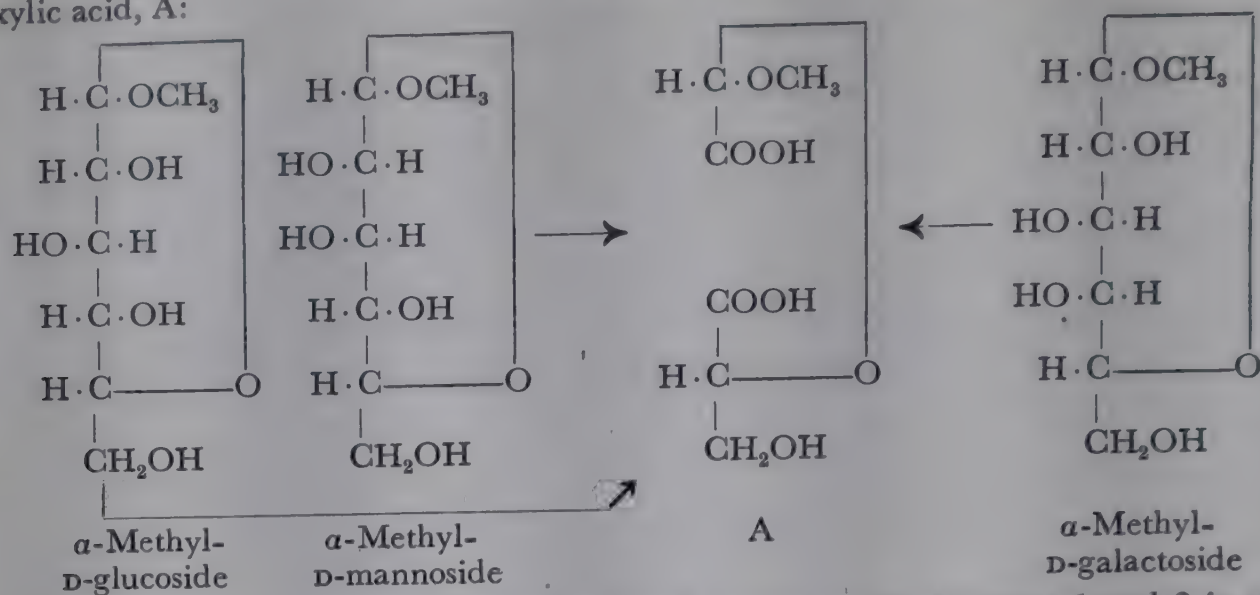
Experiments with α - and β -glucose have shown that the conductivity of a solution of boric acid containing α -glucose falls immediately after the two components are brought together, whereas in the case of a solution of boric acid containing β -glucose it rises. There must therefore be two hydroxyl groups in the *cis*-position (formula A) in α -glucose but not in β -glucose (formula B). As the rearrangement of α - into β -glucose, and that of β - into α - proceeds, the conductivities of the two solutions become gradually equal.

On the basis of our knowledge of the configuration of α -D-glucose the configurations of α -D-mannose and α -D-galactose can also be established since, according to Hudson,



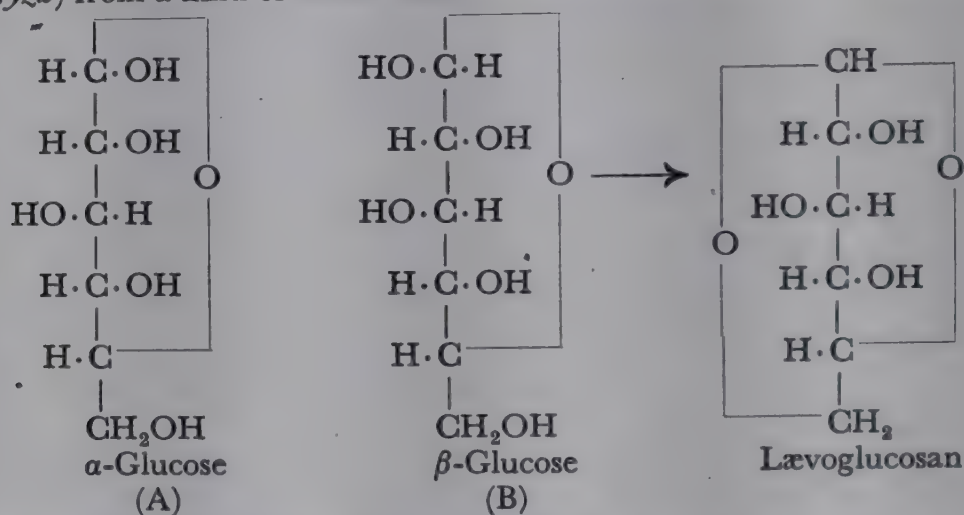


the methylglycosides of these three sugars are split by periodic acid into the same dicarboxylic acid, A:



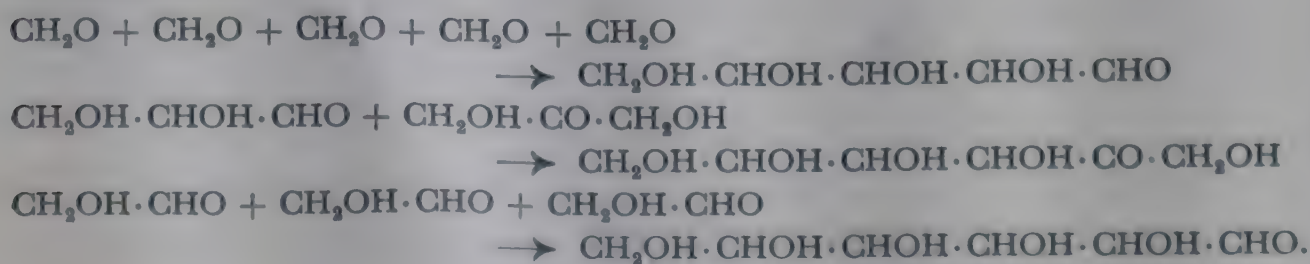
Hence, α -D-mannose contains the hydroxyl groups on the C-atoms 1 and 2 in the *trans*-, α -D-galactose in the *cis*-position.

β -Glucose (probably also α -glucose) gives partly a glucose anhydride, lævoglucosan, on distillation, which has also been found in enzymatic hydrolysates (micro-organism *Aspergillus oryzae*) from a kind of maize starch:



The elucidation of the configurational relationships between the sugars is due in the first place to the pioneer work of E. Fischer. Throughout there is excellent agreement between the requirements of theory and the results of experiment, as the above work shows. A summary of the relationships between the natural aldoses is given in the table on pp. 340, 341.

Synthesis of the natural sugars. The action of alkalis on formaldehyde (Loew), on a mixture of glyceraldehyde and dihydroxyacetone (so-called glycerose), which is obtained by oxidation of glycerol (E. Fischer), and also on glycolaldehyde (Fenton) leads to mixtures of various sugars called *formose*. These can be formed from the aldehydes mentioned by means of single or multiple aldol condensations:

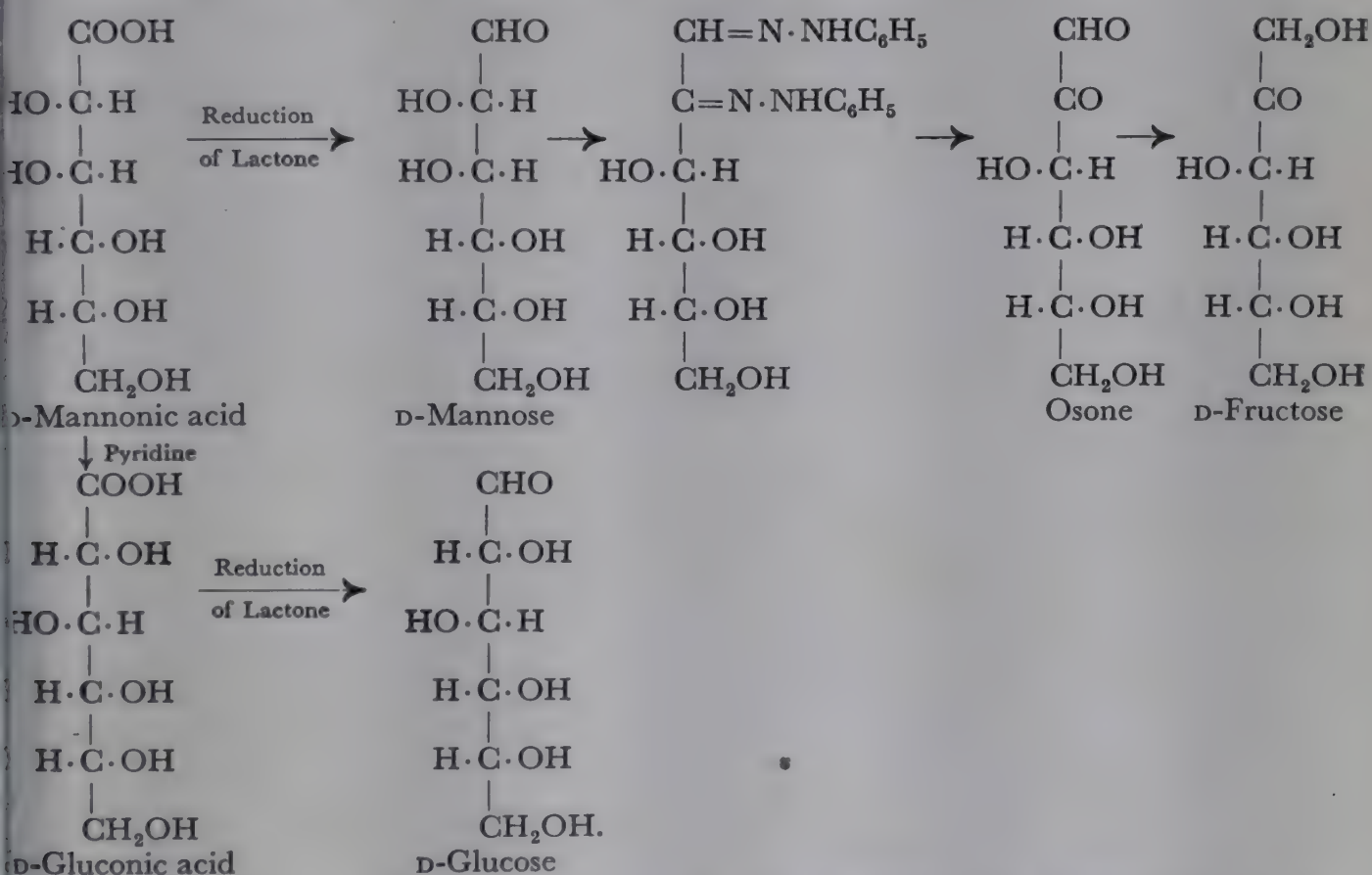


In addition to aldoses, "formose" also contains large amounts of ketoses. These are probably produced from the former during the reaction by isomerization, since, as has been mentioned on p. 328 ff., alkaline-earth hydroxides bring about the mutual transformation of aldoses and ketoses. There is, however, also the possibility that the polymerization of formaldehyde takes place in other ways, e.g. by a type of benzoin condensation (see Ch. 36), which could also give rise to ketoses:

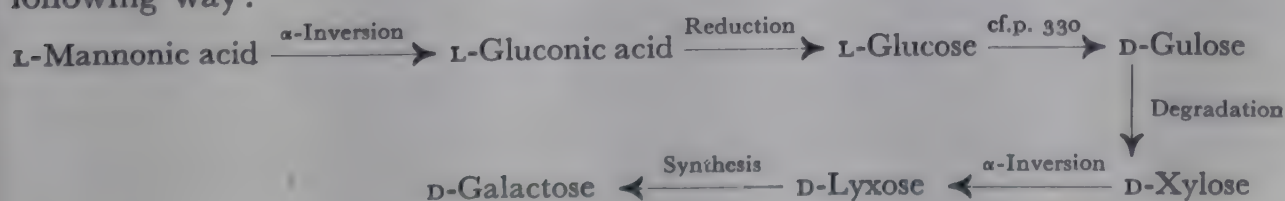


From this sugar syrup it is possible to obtain a well-crystallized osazone, called *α-phenylacrosazone*. It has been shown to be the phenylosazone of *inactive fructose*, since by the action of hydrochloric acid it gives an osone which can be reduced to inactive fructose. The DL-fructose has been further reduced by E. Fischer to DL-mannitol, and the mannitol converted by oxidation into DL-mannonic acid, and the latter has been resolved into its optically active forms.

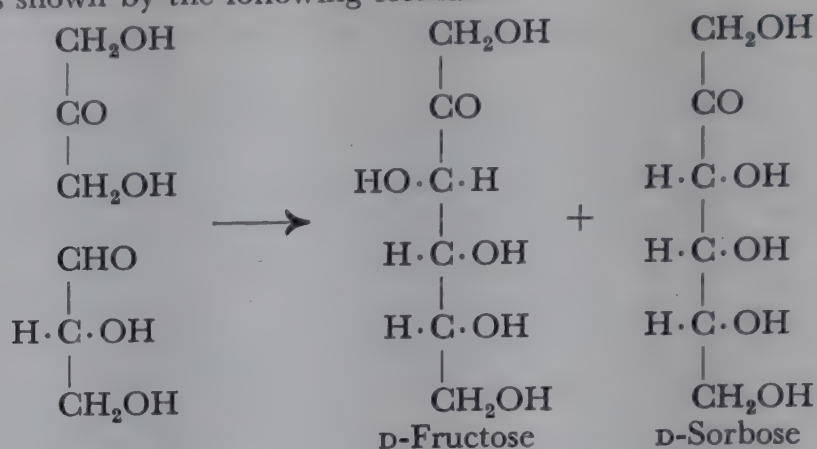
From D-mannonic acid it is now possible to pass to the naturally occurring sugars by a series of reactions already known from the foregoing work: Reduction of D-mannonic lactone yields D-mannose. If D-mannonic acid is *α*-inverted by heating with pyridine, D-gluconic acid is formed, of which the lactone gives D-glucose on reduction. The D-glucose and D-mannose thus formed can be converted into D-fructose through the osazone and osone:



L-Mannonic acid can be converted into D-xylose and D-galactose in the following way:



Fructose and *sorbose* can also be synthesized in a very simple way directly from glycer-aldehyde. E. Schmitz has obtained the two sugars in the DL-forms from DL-glyceraldehyde by the action of very dilute alkali, and H. O. Fischer has carried out the process with D-glyceraldehyde and has obtained D-sorbose and D-fructose. In this reaction, apparently part of the glyceraldehyde first rearranges to dihydroxyacetone, and then the aldol condensation occurs as shown by the following formulæ:



Detection of sugars. The separation of the sugars as their phenylhydrazones or phenylosazones is suitable for characterizing the sugars. Some phenylhydrazones, e.g. that of mannose, are very difficultly soluble in water, so that mannose phenylhydrazone can be conveniently separated from the easily soluble hydrazones of glucose and other sugars by making use of this property.

The quantitative estimation of the sugars may be carried out polarimetrically, or by fermentation with yeast (volumetric determination of the carbon dioxide formed), or by the reduction of Fehling's solution. The *reducing* sugars (cf. on the other hand, cane sugar) precipitate from the latter a definite amount of cuprous oxide, which can be estimated gravimetrically, or more simply by the method of Bertrand, in which it is dissolved in ferric sulphate solution and the ferrous sulphate produced is titrated with potassium permanganate. It is also possible to titrate the blue, hot Fehling's solution with a solution of the sugar until it is decolorized. The amount of sugar present and the weight of cuprous oxide precipitated are not exactly parallel; special tables have been compiled which show the quantitative connection between the two.

Aldoses are oxidized by alkaline solutions of iodine (hypoiodite), but ketohexoses are not (ketopentoses, however, may be oxidized under certain circumstances). It is therefore possible to determine aldoses in the presence of ketoses by such an iodine titration (Willstätter-Schudel).

Individual monosaccharides (see also glycolaldehyde, glyceraldehyde, and dihydroxyacetone, and the table on pp. 340 and 341).

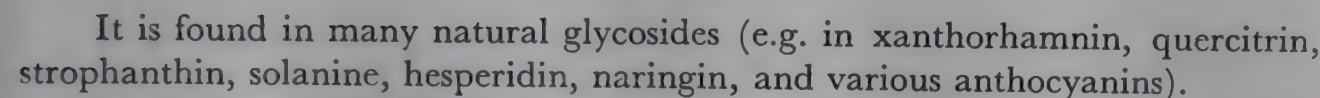
1 **TETROSES.** D- and L-erythrose are formed by the degradation of D- and L-arabonic acid, respectively; they show mutarotation. D-Threose is obtained in an analogous way by the degradation of D-xylonic acid, and L-threose by the degradation of L-xylose by Wohl's method (through the oxime and nitrile). The ketose of this series is erythrulose, $\text{CH}_2\text{OH}\cdot\text{CHOH}\cdot\text{CO}\cdot\text{CH}_2\text{OH}$, of which the D-form has been obtained from D-erythritol by the action of the sorbose bacterium.

2. **PENTOSEs.** These carbohydrates are widely spread in nature in the form of polysaccharides, called pentosans. In the vegetable kingdom they occur in wood, in all the woody parts of plants (straw), in many kinds of gums, seed-cases, in lichens, fungi, and sea-weed. The pentoses are produced from them by hydrolysis. In addition there are many glycosides of which the sugar constituent is wholly or partially composed of pentoses. In the animal kingdom, these sugars are occasionally found in the urine. With human beings DL-arabinose is occasionally excreted (pentosuria) and in other cases L-xyloketose. D-Xylose has been isolated by hydrolysis of pancreas and liver, L-xylose in small quantities from

L-Arabinose. This substance occurs abundantly in cherry gum, and gum arabic, and is usually obtained by the acid hydrolysis of the former (Kiliani). It melts at 160°. The freshly-prepared aqueous solution shows mutarotation. The specific rotation decreases until it reaches the constant value $[\alpha]_D = +105^\circ$. The *p*-bromophenylhydrazone and the diphenyl-hydrazone are suitable for characterizing the substance.

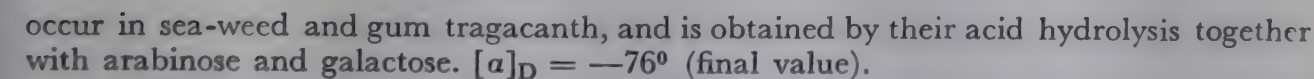
D-Xylose (wood sugar) is obtained by the hydrolysis of xylan, which is found in large quantities in wood and straw. It melts at 154°, and tastes sweet. It mutarotates, the rotation decreasing. The final rotation amounts to $[\alpha]_D = +19^\circ$.

L-*Rhamnose*. This methylpentose has the configuration:



Its hydrate, $C_6H_{12}O_5 \cdot H_2O$, melts at 93° , the anhydrous substance at $122-124^\circ$, $[\alpha]_D = +8.4^\circ$ (final value). In alcoholic solution, the sugar is lævorotatory. It is usually prepared by hydrolysis of xanthorhamnin or quercitrin.

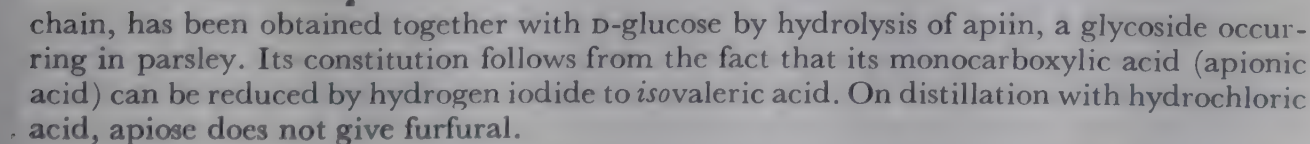
According to a proposal due to Votoček, the methylpentoses are systematically named after the hexoses with which they have common configurations (i.e. the same spatial positions of H and OH at the asymmetric carbon atoms). To the name of the hexose, the term "methylose" is added. Thus L-rhamnose would be called L-mannomethylose, and D-fucose would be called D-galactomethylose.



D-Fucose, or *rhodose*, was discovered by Votoček in glycosides contained in *Convolvulaceae*. It melts at 144°. Crystalline rhodose occurs in the α -form. $[\alpha]_D = +127.0^\circ \rightarrow 76.3^\circ$.

Digitalose (from digitalis glucosides) is 3-methoxy-D-fucose; the methylation products of digitalose and D-fucose are identical. There are also other natural methyl ethers of sugars having the methoxy-group in the 3-position (cymarose, diginose, etc.).

Quinovose, or *D-glucomethylose*, is a methylpentose which occurs as a glycoside (quinovin) in cinchona barks.



3. **HEXOSES.** The hexoses occur very widely in the free state in natural products, though in comparatively small quantities. On the other hand, they are found in immense amounts as components of the oligo- and polysaccharides, and also in many glycosides.

D-Glucose, grape sugar, dextrose. In the free state, this sugar often accompanies cane sugar (sucrose) in plants. Sweet fruits are particularly rich in it. The animal and human organism contains small amounts of glucose in the blood, in the cerebrospinal fluid, and in lymph. In certain pathological conditions (Diabetes mellitus) it occurs in the urine in large quantities. Very much D-glucose takes part in the building up of di- and polysaccharides; malt sugar, cellobiose, starch, and cellulose are made up completely from glucose. In cane sugar and lactose it occurs together with other monosaccharides, and it is obtained from a large number of glucosides by hydrolysis.

D-Glucose is the most frequently and best investigated of the monosaccharides. It is known in the α - and β -forms. Ordinary glucose consists chiefly of α -glucose. The latter melts at 146.5° , $[\alpha]_D = +109.6^\circ$ (initially). β -Glucose is best made by heating the α -form in pyridine. Its specific rotation is $+20.5^\circ$, and melting point $148-150^\circ$. In aqueous solution the final value of the rotation of glucose after mutarotation has occurred is $+52.3^\circ$. It is fermented by yeast.

The detection of glucose in the presence of other sugars is usually based on its oxidation to saccharic acid. This is detected by its formation of a difficultly soluble acid potassium salt.

D-Mannose. This substance occasionally occurs in the free state in plants (*Amorphophallus Konjak*, orange skin), but more often in the form of "mannosides", i.e. glycosides of mannose.

Polysaccharides known as *mannans*, which give mannose on hydrolysis are very abundant; the seed-cases of the ivory nut (*Phytalephas macrocarpa*), the carob bean, yeast gum, and sea-weed are rich in them.

Mannose is easily separated from its solutions by making use of the fact that its phenylhydrazone is sparingly soluble and crystallizes well. The sugar melts at 132° , tastes sweet, and is fermented by yeast. It is known in an α -form (specific rotation in water $+30^\circ$) and in a β -form (specific rotation -17°). $[\alpha]_D$ for the equilibrium mixture of the two isomers in water is $+14.5^\circ$.

Ordinary mannose has a δ -oxide ring, but γ -derivatives are also known.

D-Galactose. Complex polysaccharides containing galactose called *galactans* are abundant amongst the reserve carbohydrates in the nutritive tissue of seeds, and in certain kinds of gum. D-Galactose is also a component of lactose, the trisaccharide raffinose, the tetrasaccharide stachyose, and many glycosides (e.g. xanthorhamnin, digitonin). It is interesting to note that galactose derivatives also occur in the cerebroside of the brain (e.g. in kersin).

The sugar crystallizes with one molecule of water of crystallization, and when anhydrous melts at 164° $[\alpha]_D = +81^\circ$ (final value). It can be fermented. To estimate it in the presence of other monosaccharides it is usually oxidized to mucic acid. Galactose methyl-phenylhydrazone is difficultly soluble.

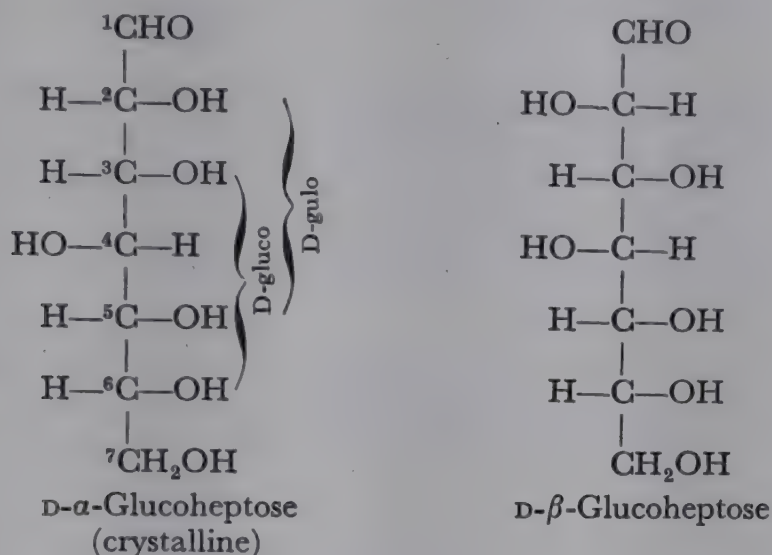
D-Fructose, or fruit sugar, is found in the free state in plants, particularly in sweet fruits, and in honey. It is a component of sucrose, and is the parent substance of the polysaccharide inulin, which, on hydrolysis gives entirely D-fructose.

The compound tastes sweet and is fermented by yeast. It melts at about 100° . The aqueous solution is laevorotatory ($[\alpha]_D = -93^\circ$), and the sugar is therefore sometimes called laevulose. To detect D-fructose in the presence of other sugars its precipitation as the difficultly soluble double compound with calcium hydroxide, $(C_6H_{12}O_6 \cdot Ca(OH)_2 \cdot H_2O)$,

may be used. The two components of a mixture of an aldose and a ketose (e.g. glucose and fructose) can be determined by titrating an aliquot part with Fehling's solution, and oxidizing another portion with sodium hypoiodite. Both aldose and ketose are oxidized by the Fehling's solution, but the hypoiodite only oxidizes the aldose. The difference between the two determinations thus gives the amount of ketose present.

L-Sorbose is produced in the juice of the berries of the mountain ash from sorbitol by the oxidizing action of the sorbose bacterium. It tastes sweet and melts at 165° , $[\alpha]_D = -42.9^{\circ}$. Sorbose is not fermented by yeast.

4. **HEPTOSES.** Heptoses were first obtained by synthesis from hexoses. Thus, from *D*-glucose two epimeric glucoheptoses, α - and β -, are formed, of which the first gives an inactive, and the second an active pentahydroxypimelic acid on oxidation. Their configurations are therefore:

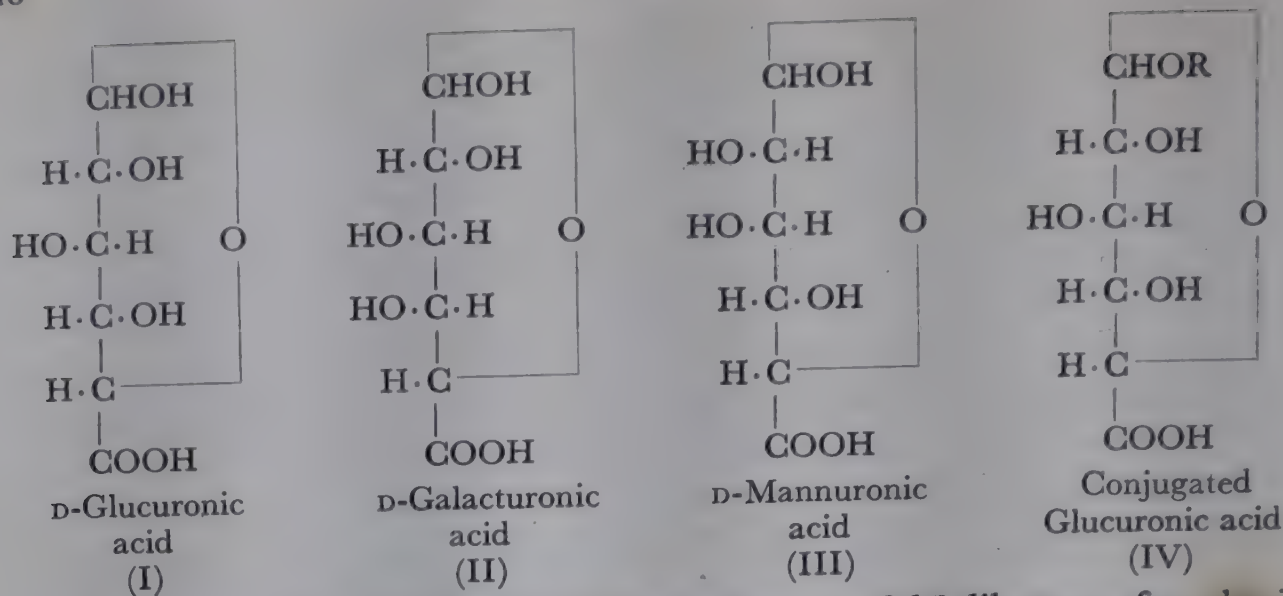


According to the nomenclature suggested by C. S. Hudson, the names of the heptoses are composed of those of two hexoses, whose asymmetric C-atoms correspond in their configuration to the asymmetric C-atoms 6 to 3, and to the C-atoms 5 to 2 of the heptose, respectively. Thus, α -glucoheptose is called *D*-gluco-*D*-guloheptose.

A *mannoketoheptose* has been isolated from the Avocado pear (fruit of *Persea gratissima*), in which it occurs together with perseitol. Its melting point is 182° , and $[\alpha]_D = +29.3^{\circ}$. It is not fermented by yeast. Another ketoheptose, *sedoheptose* or *sedoheptulose*, has been found in a *Crassulacea* (*Sedum spectabile*). It is a syrup which cannot be fermented. Its phenylosazone melts at 197° . The sugar is a ketose (*D*-altroheptulose).

5. **OCTOSES, NONOSES, AND DECOSES** have been prepared by synthesis from hexoses (glucose and mannose). It is interesting to note that mannnonose can be fermented but not glucononose.

6. **Glucuronic acid. Galacturonic acid. Mannuronic acid.** Aldehydo-carboxylic acids of the sugar series occur fairly abundantly in nature. They are known under the name of *uronic acids*. That which has been known for the longest time is *D*-glucuronic acid (I) which occurs in the animal organism conjugated with phenols or alcohols (formula IV). Thus, human urine normally contains some phenol-glucuronic acid and indoxyl-glucuronic acid, whilst that of cows which have eaten mango leaves contains a condensation product of glucuronic acid and euxanthone, viz. euxanthic acid (see Ch. 42), etc. Glucuronic acid is also used by the organism to render innocuous harmful substances, which combine with the acid, and are in this way removed from the organism. Thus trichloroethyl alcohol is removed as urochloral acid, a condensation product with glucuronic acid. Menthol is also removed from the body in the form of an analogous conjugated compound.

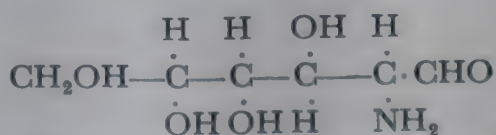


Glucuronic acid can be obtained by the reduction of the dilactone of saccharic acid. Usually, however, the "conjugated" glucuronic acids excreted in the urine (euxanthic acid, menthol-glucurone, etc.) are used for this preparation. Free glucuronic acid is syrupy, but it forms a crystalline lactone. On heating with hydrochloric acid it decomposes into furfural, carbon dioxide, and water, thus giving the reactions of a pentose.

D-Galacturonic acid (II) is a constituent of pectin (F. Ehrlich). The α -form, $\text{C}_6\text{H}_{10}\text{O}_7 \cdot \text{H}_2\text{O}$, crystallizes in white needles, m.p. 156–159°, $[\alpha]_{\text{D}}^{20} = +98.0^\circ$ (water). The β -isomeride also forms needles, m.p. 160°, $[\alpha]_{\text{D}}^{20} = +27.0^\circ$. The final rotation in aqueous solution after mutarotation is $+50.8^\circ$.

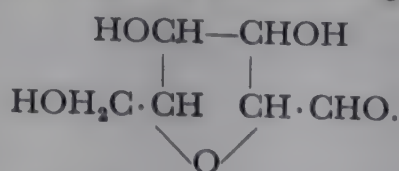
D-Mannuronic acid (III) can be obtained from the lactone of *D*-mannosaccharic acid by reduction with sodium amalgam (K. P. Link). The β -form melts at 165–167°; $[\alpha]_{\text{D}}^{25} = -47.9^\circ \rightarrow -23.9^\circ$. The α -form sinters at 110° and becomes dark in colour at 120°, $[\alpha]_{\text{D}}^{25} = +16.0^\circ \rightarrow -6.05^\circ$. *D*-Mannuronolactone melts at 142°.

7. Amino-sugars. Some years ago Ledderhose isolated a nitrogenous substance by the hydrolysis of chitin, which resembled the carbohydrates in many respects. It is called *glucosamine* or *chitosamine*. Analysis gives the formula $\text{C}_6\text{H}_{13}\text{O}_5\text{N}$, and this, combined with the fact that glucosamine gives the same osazone as glucose and mannose with phenylhydrazine acetate, gives its constitutional formula. It is to be regarded as an α -aminohexose, only the configuration at the α -carbon atom remaining in doubt. This last uncertainty has been solved by indirect evidence (comparison of peptides containing glucosaminic acid with those from *D*- and *L*-amino-acids as regards sensitivity to enzymic attack; comparison of the rotatory dispersion curves of the copper salt of glucosaminic acid with those of *D*- and *L*-amino-acids). The concordant results of these investigations establish for glucosamine the configuration of *D*-glucose (position of the amino-group as in the *D*-amino-acids). Hence the spatial structure is given by the following formulation:



This formulation is confirmed by a synthesis of glucosaminic acid, the oxidation product of glucosamine, by E. Fischer and Leuchs, who obtained it by the addition of ammonia and hydrocyanic acid to *D*-arabinose, and hydrolysis of the aminonitrile produced.

It is possible, by suitable reactions, to convert glucosamine into glucose or mannose. Nitrous acid, on the other hand, gives a non-crystallizable syrup called *chitose*, which may consist chiefly of an anhydro-sugar of the following constitution:



(hydroxymethyl-dihydroxy-tetrahydrofurfural).

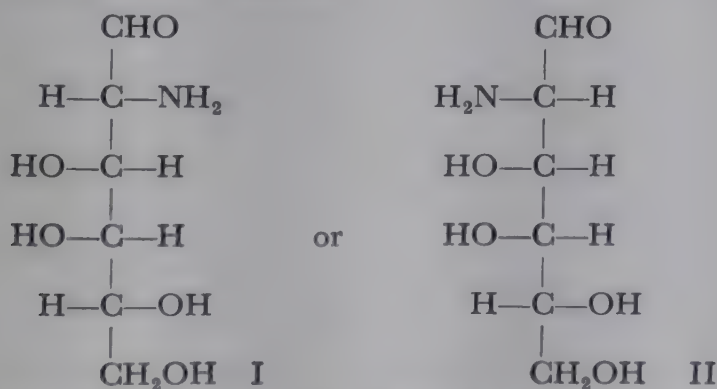
Glucosamine hydrochloride crystallizes beautifully, is readily soluble in water, and shows mutarotation, $[\alpha]_{\text{D}}^{20} = +72.5^\circ$ (final value). Like the sugars, it reduces Fehling's solution. Free glucosamine is obtained from the hydrochloride by the reaction with diethylamine in alcohol. It is readily soluble in water, giving a strong alkaline solution, and cannot be preserved for very long.

Chitin, the parent substance of glucosamine, has the characteristics of a complex polysaccharide. It is fairly abundant in nature, occurring as the skeletal substance of arthropods, molluscs, brachyopods, and bryozoa, and is also found in worms and bacteria. In the vegetable kingdom it is found in fungi and lichens. It occurs comparatively pure in lobster shells and in the wing-cases of the cockchafer.

Powerful acid hydrolysis breaks up chitin completely into glucosamine and acetic acid. By partial degradation chitobiose (as octaacetate) and N-acetylglucosamine have been isolated as intermediate products, from which it follows that the acetyl radicals contained in chitin must be, at least partly, linked with nitrogen. Treatment with strong alkalis brings about quite a different reaction. It gives acetic acid and *chitosan*, a substance which still resembles chitin, but possesses weak basic properties, since it can form crystalline salts. Nitrous acid converts it completely into *chitose* (see above).

In the gastro-intestinal tract of the snail there are enzymes — chitinases — which attack both chitin and chitosan. From chitin, N-acetylglucosamine is formed to the extent of 80 per cent. Chitosan is broken down into lower polyglucosamines.

CHONDROSAMINE is an aminohexose isomeric with chitosamine. It is a product of hydrolysis of chondroitin sulphuric acid (see below). The compound has also been synthesized from lyxose (Levene). It has been shown, in a similar way as for glucosamine, that of the two formulæ I and II, both possible on the basis of synthesis, the first (i.e. that of 2-aminogalactose) represents chondrosamine.



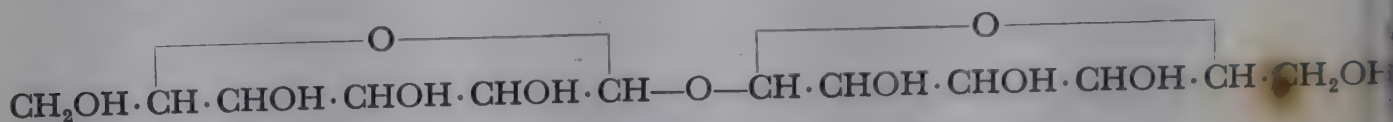
Treatment of chondrosamine with bromine water gives chondrosaminic acid (monocarboxylic acid).

Chondroitin sulphuric acid is found in cartilage, and breaks down on hydrolysis

into chondrosamine, glucuronic acid, acetic and sulphuric acid. Related substances have been detected in the gastric mucosa and in that of ovarian cysts, etc.

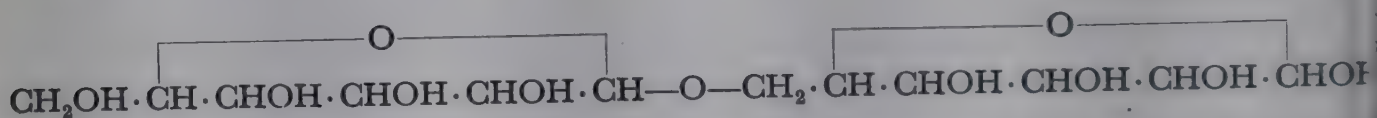
II. Oligosaccharides

The combination of monosaccharides to form di- and oligosaccharides takes place according to the principle of the formation of glycosides, the acetal-hydroxyl group of the one sugar molecule linking up with a hydroxyl of another monosaccharide molecule, with elimination of water. If the latter also participates in the formation of the disaccharide with its acetal-hydroxyl group, a new sugar of the type



is formed. It no longer has a free aldehyde group, and therefore does not reduce Fehling's solution. The disaccharides of this group, to which belong trehalose, isotrehalose, and sucrose (cane sugar), are also sometimes called "trehalose sugars".

If, however, the second monosaccharide molecule takes part in the anhydridization process with any of its *alcoholic* hydroxyl groups, oligosaccharides are formed in which there is still a free aldehyde or keto-group, and which, therefore, like the simple sugars, give cuprous oxide with Fehling's solution. They are disaccharides of the gentiobiose type, e.g.:

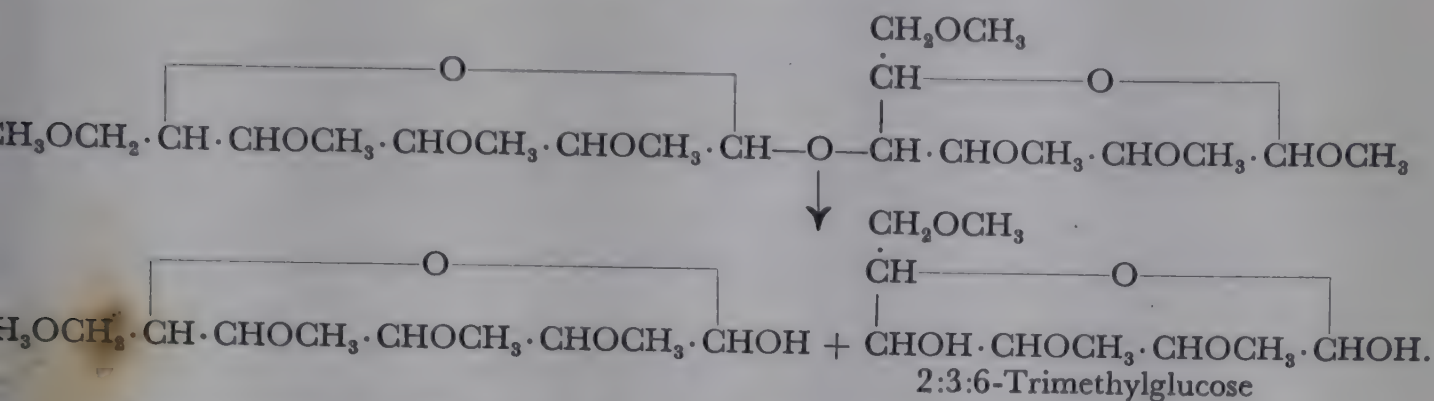


Even if the two monosaccharide residues of the disaccharide are identical there are several possibilities of isomerism, since the first molecule can combine with the second by means of *different* hydroxyl groups. Also, theory predicts the existence of α - and β -forms for each disaccharide corresponding to the α - and β -forms of glucose and the glycosides, of which the existence depends on the fact that the first and second sugar residues can occur in either the α - or the β -configuration. Finally, molecules not of the same type often combine; thus, different pentoses and hexoses combine to give higher sugars, so that a very large number of compounds is, in this respect, also possible.

The investigation of the structure of an oligosaccharide always begins with a hydrolytic fission. This can be brought about by acids, or often with enzymes, and gives the constituents of which the higher sugar is made up. For those oligosaccharides that occur in nature it is always possible to find enzymes which will split them up. They usually act specifically on the substrate concerned. Their names are derived from the sugars which they hydrolyse (saccharase hydrolyses saccharose (cane sugar), lactase hydrolyses lactose (milk sugar) etc.).

Simple hydrolysis can, of course, give no information about the kind of union of the individual components in the polysaccharide. A process which often serves this purpose depends on first methylating the hydroxyls of the polysaccharide, and then carefully hydrolysing the methylated compound. Methylated monosaccharides are thus obtained, of which the constitution can be determined (Haworth, Irvine). Their hydroxyl groups which have not been methylated must

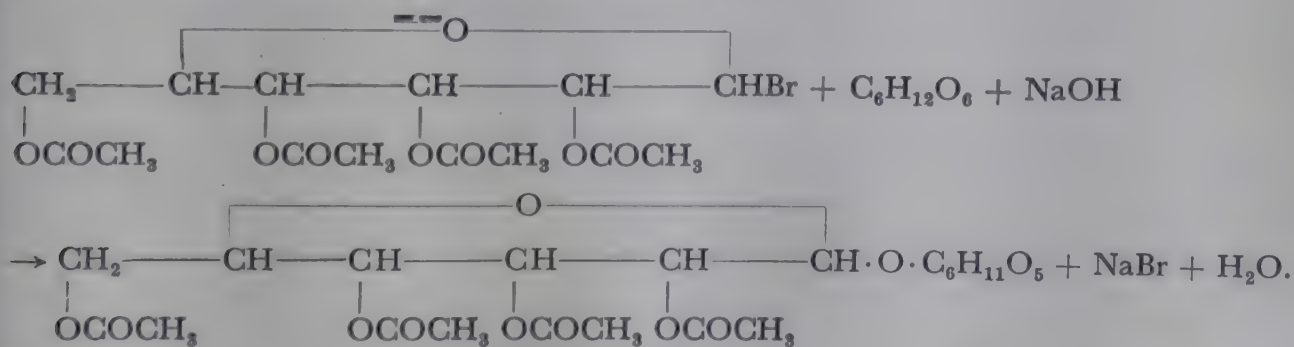
be those which were used in linking the simple sugar residues in the polysaccharide. Thus, a methylated 4-glucosidoglucose gives on hydrolysis, tetramethylglucose and 2:3:6-trimethylglucose (The carbon atoms of the sugars are indicated by numbers which begin at the aldehydic carbon atom, or in the case of ketoses at the end of the molecule at which the carbonyl group is situated):



OCCURRENCE AND SYNTHESSES. Several di-, tri-, and tetrasaccharides occur in the free state in plants, sucrose being particularly abundant. Gentianose occurs in gentian root, melecitose in some kinds of manna, raffinose in sugar beet, stachyose in *Stachys tubrifera*. Amongst the glycosides containing disaccharides as the sugar component are amygdalin and crocin (both with gentiobiose as the sugar), xanthorhamnin (with rhamnose), several flower pigments, strophanthin, etc. Finally, disaccharides form the basis of several polysaccharides. Maltose is obtained from starch, and cellobiose from cellulose by degradation.

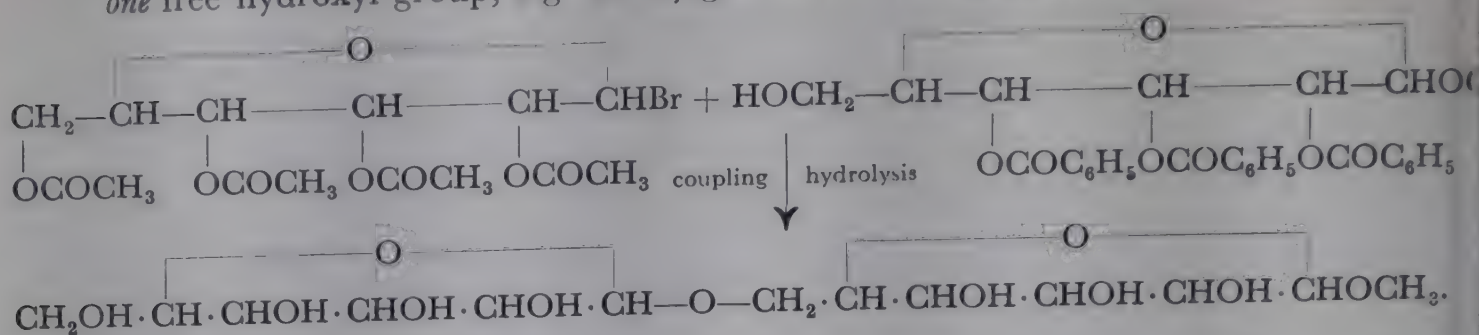
A number of disaccharides have been synthesized. Bourquelot and Hérissé, Bridel, and Aubry, have been particularly successful in this direction using enzymes. Enzymes, under suitable conditions can build up from their components the same disaccharides which they hydrolyse. Thus emulsin, in concentrated solutions of glucose, builds up gentiobiose and (in small quantity) cellobiose. Lactobioses have also been synthesized in a similar way. Newer enzymatic syntheses of disaccharides are based on the action of appropriate phosphatases on glucose-1-phosphate and a monosaccharide in aqueous solution. Thus, the phosphatase from the bacterium *Pseudomonas saccharophila*, in a solution containing glucose-1-phosphate and fructose, forms sucrose (cane sugar): Glucose-1-phosphate + Fructose \rightleftharpoons sucrose + inorganic phosphate (W.Z. Hassid and co-workers).

E. Fischer has devised a purely chemical method which can give disaccharides. Acetobromoglucose (see p. 328) is made to react with monosaccharides in alkaline solution, when acetyl derivatives of the disaccharides are formed. These can then be hydrolysed to the free sugars:



The value of this procedure is, however, limited by the fact that it often

appears to give mixtures of a number of oligosaccharides. This can be avoided by coupling the acetobromoglucose with a sugar derivative which possesses only *one* free hydroxyl group, e.g. methylglucoside tribenzoate (Helferich):



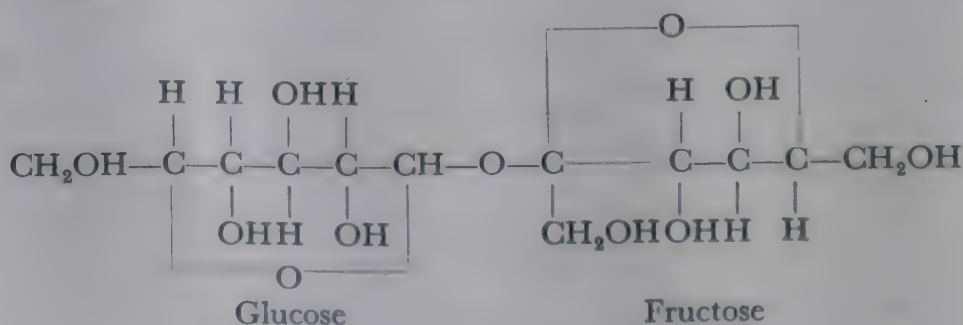
The substance thus synthesized is a methylgentiobioside (cf. gentiobiose).

Individual oligosaccharides

A. Disaccharides, SUCROSE, CANE SUGAR (saccharose). This sugar which is of great economic importance as a sweetening substance and a food, is found very abundantly in the vegetable kingdom. Most plants probably contain at least small amounts of it. The sugar beet and the stem of the sugar cane are very rich in it, and cane sugar is obtained commercially from them.

For this purpose the chopped beet or the sugar cane are systematically extracted with water. The cane sugar present within the cells diffuses through the cell walls into the aqueous liquid. When this has become sufficiently concentrated (12–15 per cent of sugar), lime is added, which precipitates dissolved acids (phosphoric acid, oxalic acid, citric acid) and proteins. Next to this purification of the juice follows the so-called “saturation process”, i.e. by passing in carbon dioxide the excess of lime is precipitated, and the calcium saccharate is again decomposed. When the sugar juice has been filtered from the precipitate, it is evaporated, the liquid being kept in continual motion, until a large part of the sugar crystallizes out. The mother liquors give a second crop of crystals on further evaporation. For the further purification of the sugar, it is usually recrystallized from water once again, and the solution clarified by filtration through porous charcoal. The final mother liquor, from which direct crystallization is no longer possible is called *molasses*. It is very rich in nitrogen, containing, in addition to sugar, considerable amounts of betaine, amino-acids, and simpler organic acids, and can be used for the manufacture of trimethylamine (see p. 133) or sodium cyanide (see p. 185). It is, however, also possible to obtain the residual sugar by the addition of strontium hydroxide. This combines with sucrose giving the double compound $\text{C}_{12}\text{H}_{22}\text{O}_{11} \cdot 2\text{SrO}$, which is precipitated. The precipitate is separated by centrifuging, and is reconverted into sugar and strontium carbonate by the action of water and carbon dioxide.

Sucrose is composed of D-glucose and D-fructose, into which it is decomposed by hydrolysis with enzymes (invertases or saccharases) or with acids. Its constitutional formula



has been proved by Haworth. The glucose half has a δ -oxide ring, the fructose part a γ -oxide ring.

Sucrose is dextrorotatory, $[\alpha]_D^{20} = +66.5^\circ$. Of the two monosaccharides formed by hydrolysing it, glucose rotates to the right and fructose more strongly to the left. The resultant mixture therefore rotates the plane of polarization to the left. Since the rotation is thus changed from dextro to lævo during the course of the hydrolysis, the process is also known as inversion, the enzyme which brings it about is called invertase, and the mixture of glucose and fructose produced is called invert sugar.

The hydrolysis of sucrose by acids is a classical example of a unimolecular reaction. It was studied by Wilhelmy as far back as 1850. In equal times the same fraction of the unchanged sucrose present at the commencement of each period is hydrolysed.

Sucrose does not reduce Fehling's solution and does not react with phenylhydrazine. It crystallizes excellently (monoclinic), melts at 184° , and is readily soluble in water, but difficultly soluble in alcohol. It is almost always estimated quantitatively by means of the polarimeter.

TURANOSE. This consists, like sucrose, of one molecule of glucose and one molecule of fructose, but is capable of acting as a reducing agent, and therefore must contain a free carbonyl group. It melts at 157° , $[\alpha]_D = +75.6^\circ$ (final rotation). It is very probably a 3-glucosido-fructose (3- α -glucosido- β -fructopyranose). Its parent substance is melezitose (see p. 356), a trisaccharide, from which it is formed by partial hydrolysis.

MALTOSE, MALT SUGAR, is formed from starch by the action of diastasic enzymes. Since these occur particularly abundantly in germinating barley, or malt, and this is used largely for the hydrolysis of starch, the sugar produced has received the name malt sugar. It was discovered in this way by Saussure, Payen and Persoz, and Dubrunfaut, and was also more fully investigated by them.

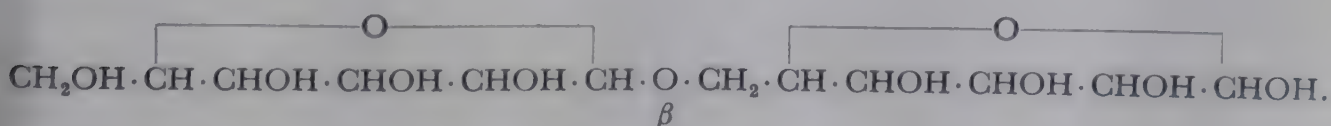
Maltose consists of two molecules of glucose, of which one molecule is attached to the other in the 4-position. The linking between the two glucose radicals is α -glycosidic. Malt sugar is therefore 4- α -glucosidoglucose (Haworth, Irvine). It is isomeric with cellobiose, which is β -glycosidic, but otherwise they have the same structure.

It reduces Fehling's solution, forms a hydrazone and an osazone, is fermented by yeast, is very readily soluble in water, but difficultly soluble in alcohol. $[\alpha]_D = +137^\circ$ (final value).

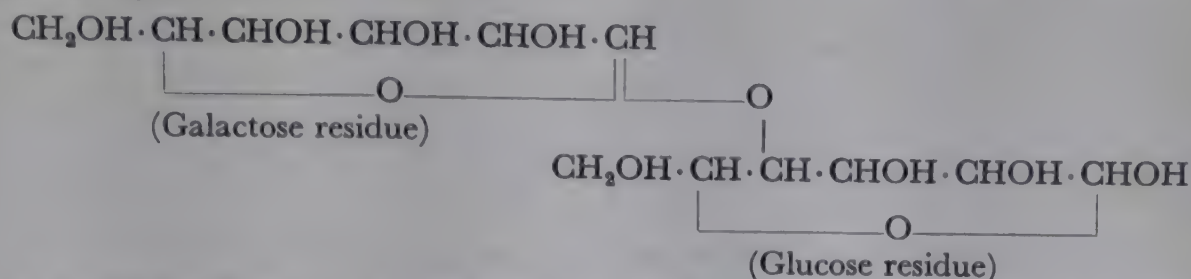
The enzymes which break it down into glucose are called maltases. They are present, for example, in yeast, in moulds, and in small quantities in malt, also in saliva, pancreatic juice, and in the intestine.

The octaacetate and heptaacetate of maltose are characteristic and difficultly soluble.

GENTIOBIOSE. This disaccharide is a 6-glucosidoglucose, in which the glucose groups are linked together as in the β -glycosides (Haworth, Kuhn, Zemplén, Hudson).



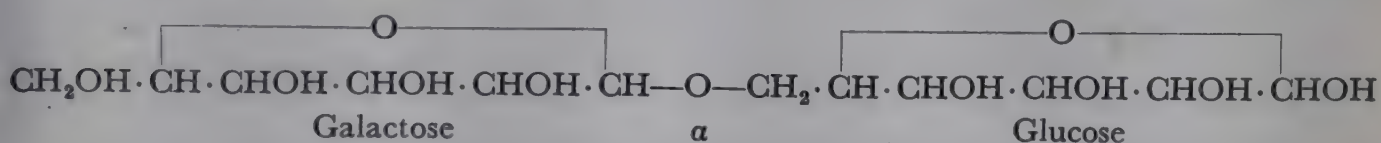
the action of acids and enzymes into glucose and galactose. Its constitution is established. The galactose radical is attached to the glucose molecule in the 4-position. The disaccharide is 4- β -galactosidoglucose; this has also been obtained synthetically.



Lactose exists in an α - and a β -form, of which the first mutarotates so that the rotation falls, whereas for the second the rotation increases. The final value of the specific rotation is $+55.3^\circ$. If lactose is crystallized at ordinary temperatures, the α -compound is formed, but above 93° , the β -isomeride crystallizes out. Lactose forms an osazone, reduces Fehling's solution, and has a sweet taste.

Enzymes which hydrolyse lactose, the lactases, are fairly abundant. They have been found in the intestinal juices of young mammals, and in those of lower animals, in certain types of yeast (lactose yeasts, kephir), and in emulsin. In the preparation of "Yoghurt" bacteria convert lactose into lactic acid.

MELIBIOSE. Like lactose, the disaccharide melibiose is made up of one molecule of galactose and one molecule of glucose. It reduces Fehling's solution, forms an osazone, and shows mutarotation (final value, $[\alpha]_D = +143^\circ$). According to Haworth it is 6- α -galactosidoglucose:



Melibiose is formed by the incomplete hydrolysis of the trisaccharide raffinose (see below). It tastes sweet. Bottom-fermentation yeasts contain an enzyme (melibiase) by which the disaccharide is hydrolysed and fermented. This is not found in top yeasts.

In addition to those disaccharides which are composed of two molecules of hexoses, those consisting of a hexose and a pentose also occur in plants. To this class belongs *vicianose*, which is made up of D-glucose and L-arabinose (6- β -L-arabinosido-D-glucose, synthesized by Helferich). It forms a constituent of the cyanogenic glycoside vicianin from vetches.

Primverose = 6-xylosidoglucose is a constituent of some glycosides, which chiefly occur in barks.

B. Trisaccharides. **RAFFINOSE**, $\text{C}_{18}\text{H}_{32}\text{O}_{16}$. This most important trisaccharide is found, though in small amounts, in the sugar beet. Molasses, in which it becomes concentrated, form a suitable material from which it may be obtained. It occurs in large quantities in eucalyptus manna.

Dilute mineral acids or yeast enzymes (raffinases) break down raffinose into fructose and melibiose (see above). Emulsin, on the other hand, breaks it down into sucrose and galactose. More powerful acid hydrolysis produces one molecule each of galactose, glucose and fructose from each molecule of raffinose.

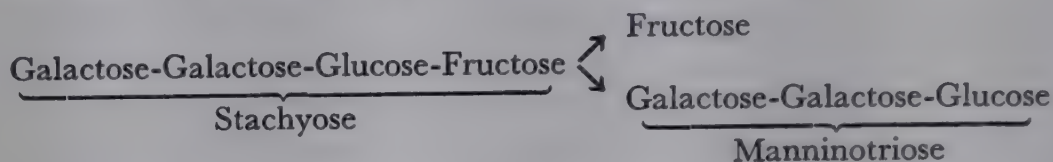
Raffinose does not reduce Fehling's solution, is stable towards alkalis and has a specific rotation of $[\alpha]_D = +104^\circ$.

GENTIANOSE, $C_{18}H_{32}O_{16}$, a trisaccharide from the roots of various kinds of *Gentiana* is made up of D-fructose and glucose. Partial hydrolysis by means of dilute acids or invertase give fructose and gentiobiose. Gentianose does not reduce Fehling's solution.

MELEZITOSE, $C_{18}H_{32}O_{16}$, is obtained from some kinds of manna. Controlled hydrolysis gives glucose and turanose (see p. 353) (Tanret, R. Kuhn). It does not react with Fehling's solution. The fructose radical stands in the middle in melezitose: glucose < fructose < > glucose.

MANNINOTRIOSE, a reducing trisaccharide from ash manna, gives on complete hydrolysis two molecules of D-galactose, and one molecule of glucose. The glucose group is at the end of the molecule and is the cause of the aldehydic properties shown by the sugar.

C. Tetrasaccharides. Pentasaccharides. STACHYOSE. The only crystalline tetrasaccharide more fully investigated at present is stachyose, $C_{24}H_{42}O_{21}$, which is found abundantly in the root nodules of *Stachys tuberifera*, in small amounts in ash manna, and in the seeds of many leguminosæ. It does not reduce Fehling's solution, and is converted by mineral acids into two molecules of D-galactose, one molecule of D-glucose, and one molecule of D-fructose. If the hydrolysis is effected by enzymes or acetic acid, D-fructose and manninotriose are formed:



Stachyose tastes slightly sweet; $[\alpha]_D = +149^0$.

VERBASCOSE from *Verbascum thapsus* (Great Mullein or Aaron's Rod), discovered by Bourquelot and Bridel, seems to be a pentasaccharide (S. Murakami), consisting of 3 molecules of D-galactose, 1 molecule of glucose, and 1 molecule of fructose, melting at 253^0 ; $[\alpha] = +170.2^0$. The sugar does not reduce and tastes sweet. Yeast splits off fructose, and emulsin removes galactose, so that the constitution of the compound is probably represented by:



Polysaccharides¹

These compounds, occurring in very large quantities in animals and plants, play the part either of reserve foods, or of skeletal substances. To the first class belong starch, glycogen, inulin, and lichenin (reserve cellulose) and the most important substance in the second class is ordinary cellulose. There are some substances which seem serve both purposes, e.g. certain mannans and galactans.

These polysaccharides differ, in part essentially, from one another in their physico-chemical behaviour. Thus, there are all stages of transition between those which are readily soluble in warm water (such as inulin and glycogen), and those which are quite insoluble (such as cellulose). Some polysaccharides of this group, such as starch or inulin, separate under suitable conditions in the spherocrystalline form. The long-discussed question as to whether these carbohydrates are amorphous or crystalline, can now be answered with certainty, largely as a result of modern X-ray spectroscopy. The majority of them are crystalline. Glycogen, however, appears to be an exception.

¹ H. STAUDINGER, *Die hochmolekularen organischen Verbindungen*. Kautschuk und Cellulose, Berlin, (1932). — H. MARK, *The General Chemistry of High-Polymeric Substances*, New York and Amsterdam, (1940). — K. H. MEYER, *Natural and Synthetic High Polymers*, New York, (1942). — ROBERT J. McILROY, *The Chemistry of the Polysaccharides*, London, (1948).

By the action of mineral acids the polysaccharides of this class break down into monosaccharides. The products of this reaction are of the greatest importance for discovering the nature of the polysaccharide. In most cases, D-glucose is the final product of complete hydrolysis; starch, glycogen, cellulose, and lichenin give only glucose on complete hydrolysis by acids. From other complex carbohydrates, mannose, galactose, fructose, or the pentoses, arabinose, xylose, and fucose, are obtained under similar conditions. The polysaccharides are often named according to the nature of the products of their complete hydrolysis, e.g. mannans, galactans, arabans.

In a few cases it is possible by choosing mild methods of degradation, to isolate intermediate products in the hydrolysis of polysaccharides. Thus, the disaccharide maltose is obtained in the hydrolysis of starch, and cellobiose in that of cellulose. These provide a first insight into the way in which the individual glucose radicals are linked in the polysaccharide molecule.

It is generally believed to-day that all these complex polysaccharides have a high molecular weight, and that their molecules consist of very many hexose radicals linked together in a chain-like fashion. In support of this there is their small solubility in water, their colloidal nature, and the fact that the first products of their hydrolysis, the dextrans, are still colloidal in nature.

The individual monosaccharide residues are conceived to be linked *glycosidically* one to another in the polysaccharide molecule, forming chains of different lengths (cf. the schematic formulæ for starch, cellulose, and inulin). Although this view appears to give on the whole a correct picture of the structure of these substances of high molecular weight, it is still not certain whether there is the same type of linkage of the sugar radicals within the glycosidic chain, how large the molecules are, and the structural arrangement of their terminal members.

All the polysaccharides of this class are insoluble in the usual solvents or form *colloidal* solutions. In the latter case, e.g. for a colloidal solution of starch, or nitrocellulose, there is the possibility that the colloidal particles are single molecules, or they may be aggregates of molecules. This question, which has been intensively studied by several methods, cannot yet be considered to have been cleared up.

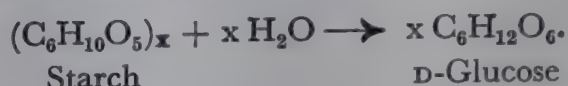
Starch.¹ Starch is the most important carbohydrate reserve of plants. It is produced from the absorbed carbon dioxide with the aid of chlorophyll, and is used as a building material in the plant itself, or in periods of considerable assimilation is stored in roots and tubers, and also in seeds (especially abundantly, for example, in potatoes and grain). Starch dissolves hardly at all in cold water, but more readily in hot water. A viscous liquid is formed, which does not reduce Fehling's solution, and which on cooling becomes gelatinous (starch paste). Starch always contains some phosphorus (0.01—0.16%), which is found in all native starches, though in varying quantities, and very probably plays a part in the enzymic degradation of starch. From the products of hydrolysis of potato starch glucose-6-phosphate has been isolated. According to the work of Maquenne, starch consists of two polysaccharides *amylose*, and *amylopectin* (surrounding part of the starch granules). The former dissolves in water without the formation of a paste and gives a pure

¹ ROBERT P. WALTON, *A comprehensive Survey of Starch Chemistry*, New York, (1928). — J. A. RADLEY, *Starch and its Derivatives*, 2nd ed., London, (1943). — RALPH KERR, *Chemistry and Industry of Starch*, New York, (1944).

blue colour with iodine. Amylopectin, on the other hand, forms a paste with hot water, and gives a violet colour with iodine. The separation of amylopectin can be carried out by extraction with alkali or by electrodialysis, that of amylose by precipitation with different organic compounds, such as esters, ketones, mercaptans, or paraffins.

The above-mentioned blue coloration which starch gives with a solution of iodine in potassium iodide (starch iodide) is regarded by some as due to the formation of a chemical compound, and by others as an adsorption phenomenon. The latter view is better supported. The starch-iodine reaction is so sensitive that it can be used to detect traces of iodine on the one hand, and of starch on the other (iodimetry). The coloration disappears when the solution is heated, but it reappears on cooling.

Even dilute acids hydrolyse starch giving glucose. The yield is quantitative under the correct conditions. Starch is therefore built up entirely of D-glucose residues. Its hydrolysis to glucose can be represented by the following simple equation:

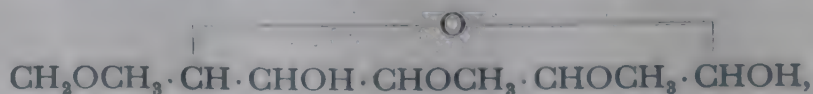


If the acid hydrolysis of starch is interrupted before it is complete, the so-called "starch dextrans" are obtained. These are colloidal substances which reduce Fehling's solution more or less strongly. They always consist of mixtures of various intermediate stages in the hydrolysis of starch. In addition to unchanged starch they contain degradation products of this polysaccharide in which aldehydic groups, the cause of the reducing action, have been set free.

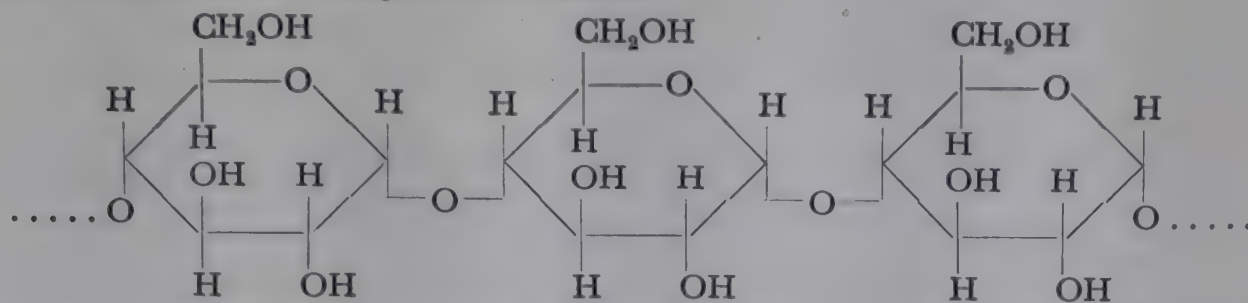
By the action of certain enzymes ("diastases" or "amylases") which are very abundant in plants and animals, occurring, for example, in germinating seeds (especially abundantly in malt = germinating barley), in saliva, and in the pancreatic juices of animals, starch is also converted into sugar. The hydrolysis does not, however, lead to glucose, but stops at the formation of a disaccharide, maltose (see p. 353). Dubrunfaut first prepared this (1847) in a state of purity, and demonstrated that it was different from glucose. The yield of maltose from starch can, under favourable conditions, reach 80 per cent or more of the theoretical amount. It follows that starch must be largely made up of maltose groups. This conclusion is particularly supported by the fact that it is also possible to convert starch into maltose derivatives by purely chemical methods. Acetyl bromide converts the polysaccharide into acetobromomaltose, a maltose derivative which can be obtained in approximately the same yield and under the same experimental conditions from maltose itself.

The degradation of starch into a derivative of maltose is also possible by oxidation with barium hypobromite, whereby maltobionic acid (the monocarboxylic acid related to maltose) is formed.

By the direct methylation of starch by means of dimethyl sulphate and alkali, or by other methods of methylation, it is possible to methylate successively all the hydroxyl groups, so that the fully methylated starch, the so-called trimethylstarch, $[\text{C}_6\text{H}_7\text{O}_2(\text{OCH}_3)_3]_x$, is obtained. The hydrolysis of this gave, in addition to about 5 per cent of 2:3:4:6-tetramethylglucose, 2:3:6-trimethylglucose



which (together with 2:3:4:6-tetramethylglucose) is also obtained by the hydrolysis of methylated maltose. W. N. Haworth has based on these facts a formula for the starch molecule, in which many glucose residues are linked together in a chain by glycosidic linkages, as in maltose:



The mixtures of simpler polysaccharides (oligosaccharides) obtained by partial hydrolysis of starch by acids can be methylated, according to K. Freudenberg, to give products from which, on distillation, non-crystallizable methyl ethers of a tri- and a tetrasaccharide are obtained. This observation also speaks in favour of a glycosidic union of numerous glucose groups in the starch molecule.

The most recent views held by different investigators (Freudenberg, K. H. Meyer, H. Staudinger) are that the two starch fractions, amylose and amylopectin, differ significantly in structure. Thus, amylose is a mixture of homologues of different degrees of polymerization (molecular weights 10,000 to 60,000), the sugar residues being linked in a chain with little or no branching. Amylopectin, on the other hand, whose molecular weight is estimated to be higher (about 50,000 to 1,000,000), is assumed to contain highly-branched molecules; the "side chains" appear to be attached to hydroxyl groups in the 6-positions of the glucose residues of the principal chain. A 6-D-glucosido-D-glucose has been isolated from starch, or from the so-called "grenzdextrins" (residual dextrins), i.e. starch fractions which are unaffected by the action of the amylase. In this connection it is to be noted that by enzymatic action amylose can be completely converted into maltose, whereas amylopectin only yields two-thirds of the theoretical quantity of maltose.

In plants (e.g. potatoes) there exist enzyme systems capable of converting glucose-1-phosphate also *in vitro* into carbohydrates, which after methylation yield the same fission products as native starch, or amylose and amylopectin, and which largely correspond to the latter substances in their other properties as well (Hanes, W.N. Haworth).

The "crystalline amyloses" are formed when *Bacillus macerans* grows on starch solutions (Schardinger). From the bacilli, cell-free enzyme solutions may be prepared, which produce from starch the same fission products. Three beautifully crystallized compounds of this group, " α -tetramylose" (α -dextrin), with the probable formula $(C_6H_{10}O_5)_6$, " β -hexamylose", presumably of the formula $(C_6H_{10}O_5)_7$, and an " α -octamylose" of unknown molecular weight, are thus formed together. Their empirical formulæ, as well as the fact that all three are hydrolysed by acetyl bromide to maltose (and acetobromomaltose) suggests that they are sugar anhydrides, composed of maltose groups.

α -Dextrin and α -octamylose are coloured blue by iodine, whilst β -hexamylose is coloured brown.

Starch is obtained commercially chiefly from potatoes, and also from various kinds of grain, such as wheat, maize, and rice. The heavier starch grains are separated from the other cell constituents by mechanical processes, usually by elutriation. In tropical countries arrowroot, starch of various plants, and also tapioca (the starch of manioc root) play an important part. Starch is chiefly used as a food. Starch paste is used as an adhesive, and rice starch as a powder.

Glycogen. This carbohydrate, which was discovered by Claude Bernard (1857) as a constituent of liver, is the reserve carbohydrate of the animal organism. It is found particularly abundantly in the livers of higher and lower animals, but is also widely spread in muscle tissue and many other cells. During muscular work the glycogen content of the muscle decreases. The carbohydrate is broken down to lactic acid through a phosphorus-containing sugar (p. 262) during the process.

According to Embden, and Meyerhof and Lohmann, first dihydroxyacetone phosphate, $\text{CH}_2\text{OH} \cdot \text{CO} \cdot \text{CH}_2\text{OPO}_3\text{H}_2$, is formed in the muscle from glycogen, probably through some active (phosphorylated) form of sugar. By disproportionation this is then transformed into *phosphoglyceric acid*, $\text{HOOC} \cdot \text{CHOH} \cdot \text{CH}_2\text{OPO}_3\text{H}_2$, and *glycerol phosphate*, $\text{CH}_2\text{OH} \cdot \text{CHOH} \cdot \text{CH}_2\text{OPO}_3\text{H}_2$. The phosphoglyceric acid is next converted into phosphopyruvic acid and pyruvic acid, CH_3COCOOH . This first stage in the sugar degradation is thus similar to that observed in alcoholic fermentation (cf. p. 89). Finally, the pyruvic acid is reduced in the muscle to lactic acid, $\text{CH}_3\text{CHOHCOOH}$, by the action of an enzyme composed of dihydrocodehydrase as the coenzyme and a protein which has been isolated in the crystalline state. The hydrogen necessary for the reduction is furnished either by the glycerophosphate, which is itself oxidized to the triose phosphate, or else by the triose phosphate itself, which is thus converted into phosphoglyceric acid.

It appears that the formation of glycogen from glucose takes place through glucose-1-phosphate. Cori found that animal tissue contains a phosphorylase which, by acting on glycogen, forms glucose-1-phosphate; the latter may be partly reconverted into a polysaccharide similar to glycogen, *in vitro*, by the same enzyme. Both the synthesis and degradation of glycogen in the living muscle therefore probably take place via glucose-1-phosphate.

Lower plants, especially the fungi, contain a substance, plant glycogen, which is very closely related to, if not identical with, animal glycogen.

Glycogen dissolves fairly easily in hot water, without forming a paste; part of the native glycogen, however, does not appear to dissolve readily in water. The colloidal solution does not reduce Fehling's solution. It is coloured violet-brown to violet-red by the addition of a small quantity of iodine. The solution rotates the plane of polarization to the right to almost the same extent as a corresponding solution of starch ($[\alpha]_D = +198^\circ$).

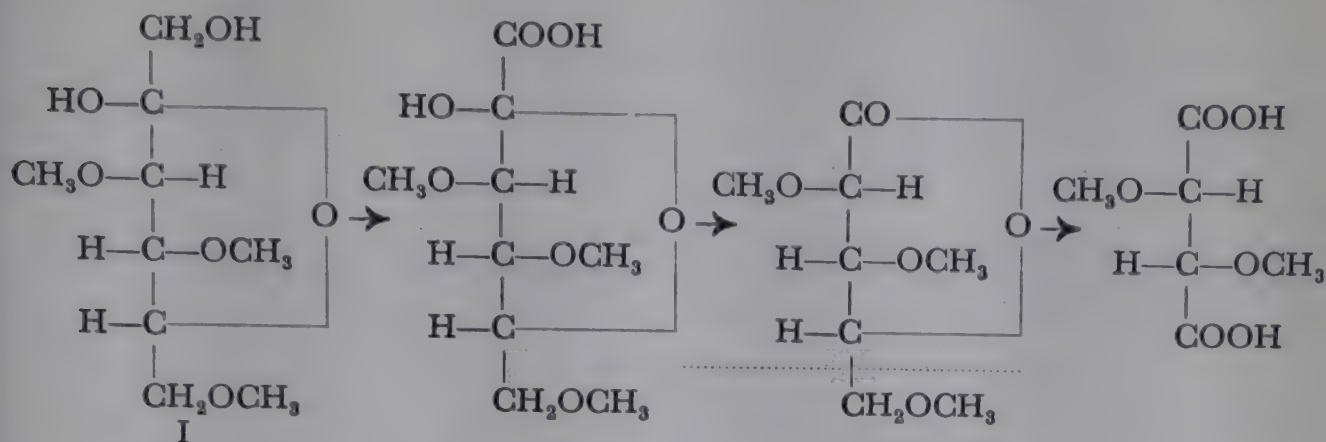
Glycogen shows considerable similarity to starch in chemical behaviour. Like the latter it is quantitatively hydrolysed to glucose by acids, and by enzymes (diastases) to maltose. *B. macerans* gives crystalline amyloses also with glycogen. The carbohydrate must therefore possess a constitution similar to that of starch. On account of the low viscosity of glycogen solutions, and for other reasons, it is assumed that the glycogen molecule is shorter and more highly branched than that of starch.

Inulin, $(\text{C}_6\text{H}_{10}\text{O}_5)_x$. Inulin occurs as a reserve substance in some plants, especially the *Compositæ*, and is often found to a large extent in their subterranean reserve stores. It is usually obtained from the tubers of Dahlias and of *Helianthus tuberosus*, and from artichokes, which are rich in this carbohydrate.

It dissolves fairly easily in water giving a colloidal solution, and does not reduce Fehling's solution. It is laevorotatory, ($[\alpha]_D = -40^\circ$) and is fairly stable towards alkalis, like starch and glycogen.

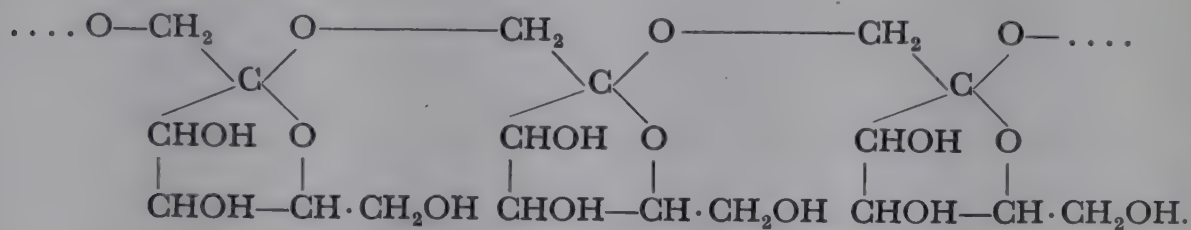
Hydrolysis by means of acids or enzymes (inulases) breaks it down completely into fructose. It is thus built up entirely from D-fructose. However, inulin does not contain the ordinary, pyranose type of fructose, since if "trimethylinulin",

obtained by the usual methods, is hydrolysed, a trimethylfructose is obtained which is shown to be 3:4:6-trimethyl- γ -fructose (I) by the following degradation reactions:



Inulin is thus derived not from the normal δ -fructose, but from γ -fructose. By the acid hydrolysis of the polysaccharide this γ -form isomerizes into the more stable δ -form.

Haworth proposes the following schematic representation for the carbohydrate, based upon the degradation of methylinulin:



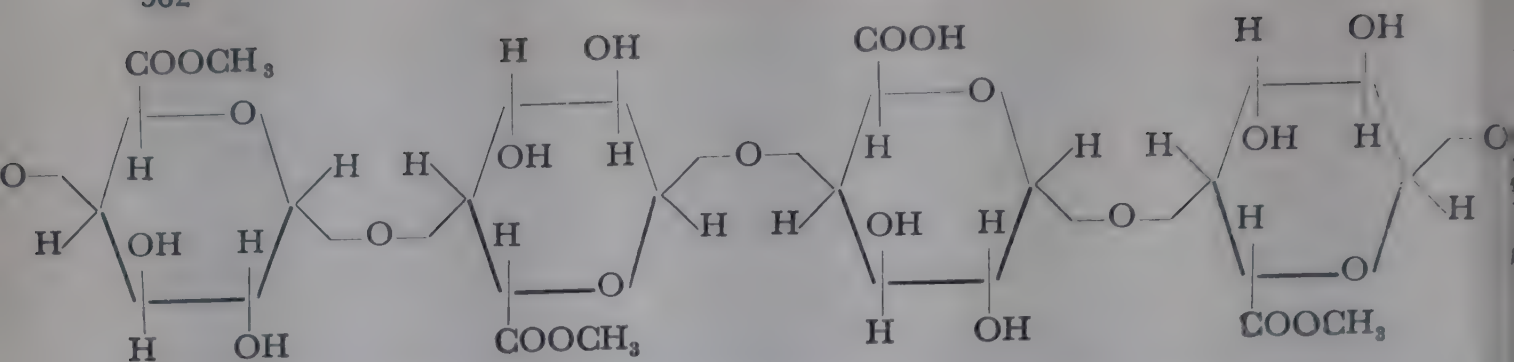
Other vegetable polysaccharides built up from fructose are *irisin*, *graminin*, and *tritacin*. These have been studied in recent times particularly by Schlubach.

Galactogen, a carbohydrate found in snails and snail eggs, consists entirely of galactose. It is amorphous, tasteless, hygroscopic, and does not give a coloration with iodine. It is not attacked by salivary enzymes.

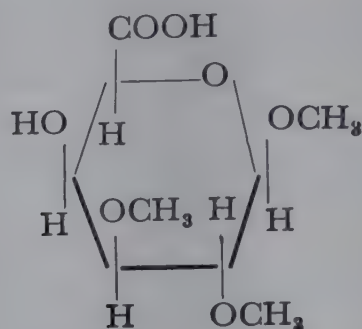
Yeast glucan and **laminarin**. Yeast glucan, a polysaccharide extracted from yeast, and laminarin, from the buds of laminaria, both give after methylation and degradation 2:4:6-trimethylglucose. Hence, in both these carbohydrates the linking of the glucose residues takes place at positions 1 and 3.

Pectins. Under this name are included gelatinizing substances which are very abundant in plants, particularly also in fruit juices (fruit jelly). Their discovery goes back to Braconnot (1825). All the pectins are high-molecular substances. Insight into their structure has only recently been obtained, thanks to the work of Felix Ehrlich, K. Link, Henglein and G. G. Schneider.

Crude pectin contains pentosans, galactosans and similar admixtures, which however, can be largely removed by repeated precipitation. Pectin purified in this way gives on hydrolysis galacturonic acid and (11.5 %) methanol. Molecular weight determinations of pectin derivatives indicate very high molecular weights. The pectins are therefore now regarded as polygalacturonic acids whose carboxyl groups are partly esterified with methyl alcohol, the structure being chain-like, as in the case of cellulose:



By degradation of methylated pectin (pectic acid), 2:3-dimethyl- β -methylgalacturonopyranoside has been isolated; this appears to confirm that a pectin unit has the structure presented in the foregoing formula (Luckett and F. Smith).



Cellulose.¹ ("skeletal cellulose"). By cellulose in the chemical sense is meant a quite definite carbohydrate which occurs exceedingly abundantly in plants as a skeletal substance, and which is broken down on total hydrolysis completely to glucose. The botanist often extends the meaning of the term "cellulose" to cover the polysaccharides which also go to make up the cell walls, such as mannans, galactans, and pentosans which contain mannose, galactose, and pentoses in addition to glucose. These latter complex carbohydrates, however, do not play the part of purely skeletal substances. They can be assimilated again in certain periods of the growth of the plant, and thus serve as reserve substances.

Of all organic compounds which occur in nature cellulose occupies the first place as regards quantity. The amount of carbon dioxide which is "fixed" in the cellulose of plants is estimated at about 1,100 billion kilograms, i.e. about half the weight of the carbon dioxide in the atmosphere. It follows that it is very important that cellulose should be quickly reconverted into its original components, carbon dioxide and water, by natural decomposition processes, so that there should not be a gradual reduction in the amount of carbon dioxide in the atmosphere. This natural decomposition is effected in the main by micro-organisms, bacteria, and moulds. Only a comparatively small amount of cellulose is decomposed in other ways (e.g. by digestion by invertebrates, burning).

Plant cellulose occurs in a very pure state in cotton.

¹ See L. HAWLEY and LOUIS E. WISE, *Chemistry of wood*, New York, (1926). — A. W. SCHORGER, *Chemistry of cellulose and wood*, New York, (1926). — H. MARK, *Physik und Chemie der Cellulose*, Berlin, (1932). — CH. DORÉE, *The Methods of Cellulose Chemistry*, London, (1933). — O. FAUST, *Celluloseverbindungen und ihre besonders wichtigen Verwendungsgebiete, dargestellt an Hand der Patentweltliteratur*, 2 vols. Berlin, (1935). — M. BATTEGAY and L. DENIVELLE, *La cellulose*, Part I and II, Paris, (1934-35). — A. G. NORMAN, *The Biochemistry of Cellulose, the Polyuronides, Lignin, etc.*, London, (1937). — E. HÄGGLUND, *Holzchemie*, 2nd ed., Leipzig, (1938). — J. T. MARCH, F. C. WOOD, *An introduction to the chemistry of cellulose*, 2nd ed., London, (1942). — E. OTT, *Cellulose and Cellulose Derivatives*, New York and London, (1943). — E. HEUSSER, *The Chemistry of Cellulose*, New York and London, (1945).

In animals, cellulose is met with in the tunicata, of which it forms the mantle or leathery skin.

Cellulose fibres possess micellar structure. They consist, as is shown by the double refraction of nitrocellulose and the X-ray diagrams of cellulose (Ambronn, Scherrer), of many, small rod-like crystallites, which are all oriented with their long axis parallel to the fibre axis. A structure is thus built up which is also characteristic of various other natural substances. It is referred to as fibrillar structure.

Cellulose is a white substance, insoluble in most liquids. It only reduces Fehling's solution in traces, and is coloured blue by an aqueous solution of iodine and zinc chloride. The best solvent for cellulose is cuprammonium hydroxide, which dissolves large amounts of it. Acids reprecipitate the cellulose. The carbohydrate is also dissolved to a considerable extent by certain concentrated hot solutions of metal salts, e.g. calcium thiocyanate, $\text{Ca}(\text{SCN})_2$; furthermore it is somewhat soluble in cold sodium hydroxide solution (-10°).

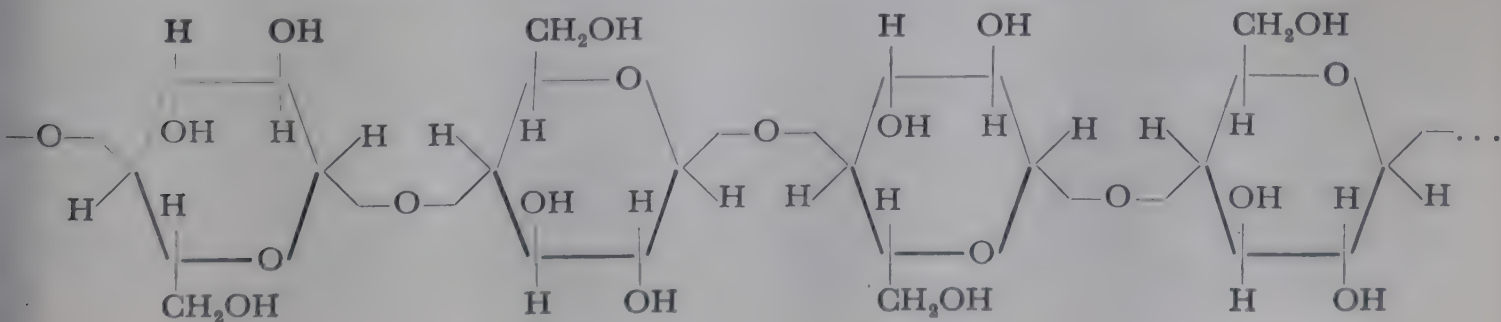
Mineral acids convert cellulose into D-glucose in almost quantitative yield on boiling. Hence D-glucose is the fundamental substance from which cellulose is built up. By acetolysis, i.e. by the action of a mixture of acetic anhydride and sulphuric acid, *cellobiose* (q.v.), an intermediate product in the hydrolysis of cellulose, is formed as its octaacetate. The yield of this, however, is always considerably less than the theoretical, and does not rise above about 40 per cent. Efforts have therefore been made to find by-products of the hydrolysis of cellulose.

R. Willstätter and L. Zechmeister succeeded in obtaining a cellotriose, a cellotetraose, and a cellohexaose in the crystalline state by the action of highly concentrated hydrochloric acid on cellulose. These taste sweet, have sharp melting points, and are dextrorotatory:

Cellotriose	$\text{C}_{18}\text{H}_{32}\text{O}_{16}$	M.p. 238°	$[\alpha]_D = +31.8^\circ \rightarrow +23.2^\circ$ (final value)
Cellotetraose	$\text{C}_{24}\text{H}_{42}\text{O}_{21}$	„ 251°	$[\alpha]_D = +11.3^\circ \rightarrow +17.0^\circ$ („ „)
Cellohexaose	$\text{C}_{36}\text{H}_{62}\text{O}_{31}$	„ 266°	$[\alpha]_D = +12.3^\circ \rightarrow +13.1^\circ$ („ „)

In addition it was possible to obtain a methylated cellotriose (decamethyl- β -methylcellotrioside), and a methylated cellotetraose (tridecamethyl- β -methylcellotetraoside) by methylation of the mixture of the lower polysaccharides obtained by the *partial* hydrolysis of cellulose. The first of these has also been prepared synthetically (K. Freudenberg).

W. N. Haworth, K. Freudenberg and others assume that the cellulose molecule consists so to speak of an extended cellobiose molecule, i.e. that in the polysaccharide there are very many glucose residues linked glycosidically in a chain in the same manner as in cellobiose (β -glycosidic with oxygen atom 4). This is shown in the following formula:



The length of the cellulose molecules is not precisely known, but it is certainly very considerable. Moreover it seems probable, that not all cellulose molecules have the same chain length, but that native cellulose consists of different "polymeric homologues".

Cellulose, $(C_6H_{10}O_5)_x$, contains three free hydroxyl groups to every six carbon atoms, and these can be methylated and esterified. Methylated cellulose has been used recently in the preparation of plastics, films, etc. The nitrates and acetates of cellulose, as well as the xanthate have been known longer, and are of outstanding importance.

CELLULOSE NITRATES (OR NITROCELLULOSES)¹, or more correctly nitric acid esters of cellulose, are obtained by the action of a mixture of nitric and sulphuric acid on wadding, cotton linters, or wood pulp. According to the conditions of nitration higher or lower degrees of nitration are reached. The cellulose nitrates most rich in nitrogen correspond approximately to the formula $[C_6H_7O_5(NO_2)_3]_x$, and therefore contain nearly three nitro-groups to six carbon atoms. They are insoluble in alcohol and ether, but are dissolved by acetone, ethyl acetate, and amyl acetate. They are very important in the explosives industry, being known as *gun-cotton*. They are gelatinized by acetone, i.e. made to swell, and in this form they are the basis for the manufacture of smokeless powder.

Nitrocelluloses of medium nitrogen content dissolve in mixtures of alcohol and ether, unlike the higher and lower nitrates. These *collodion solutions* have a limited use as adhesives, for applying small dressings to wounds, etc. Of considerably greater importance are the plastics obtained from cellulose nitrates and admixtures such as camphor. Under the name of *celluloid* they are used to-day in the manufacture of numerous articles, such as combs, brushes, buttons, toys, and particularly films. On the use of nitrocellulose in the manufacture of artificial silk, see p. 367.

CELLULOSE ACETATES² are obtained by the action of acetic anhydride and a little sulphuric acid on cellulose, or partially hydrolysed cellulose (so-called hydrocellulose); the sulphuric acid can be replaced, wholly or in part, by acid salts or zinc chloride. Also the cellulose acetates possess varying solubilities according to the method of preparation and degree of esterification. While the highest esters, the so called triacetates, $[C_6H_7O_5(COCH_3)_3]_x$, are soluble in chloroform, but not in acetone, the latter dissolves the lower and partially hydrolysed acetates. Chiefly such "acetone-soluble" cellulose acetates are used at present in the preparation of plastics similar to celluloid (*cellite*, *cellon*), for the manufacture of films, and artificial silk (*acetate rayon*). The cellulose acetates have the advantage over celluloid of being more difficultly inflammable (difficultly inflammable films).

A third cellulose ester, the XANTHATE, must be mentioned. This is formed by the action of carbon disulphide and alkali on cellulose:

¹ See also B. K. BROWN and F. M. CRAWFORD, *A Survey of Nitrocellulose Lacquer*, New York, (1928). — CHR. STARK, *Die Kollodiumwolle. Ihre Herstellung zur Verwendung für Celluloid, Kunstleder, Nitrolacke, Filme und plastische Massen*, Berlin, (1931). — OSKAR KAUSCH, *Handbuch der künstlichen plastischen Massen, System. Patentübersicht*, 2nd ed., Munich, (1939).

² D. KRÜGER, *Celluloseacetate und die anderen organischen Ester der Cellulose*, Dresden and Leipzig, (1933). — OSKAR KAUSCH, *Handbuch der Acetylcellulosen*, Munich, (1933). — E. CH. WORDEN, *Technology of Cellulose Esters*, 2nd ed., London, (1933).



Cellulose xanthate, when freshly prepared, dissolves in water to give a colloidal solution. However, the compound in solution soon breaks down with partial elimination of the xanthate radical, and re-formation of cellulose; it "ages". Hand in hand with this goes an increase in the viscosity of the solution; owing to this high viscosity the product is called "viscose". In this state it is used in the manufacture of artificial silk (viscose rayon, see p. 368).

It has already been seen that the action of mineral acids on cellulose ultimately leads to the formation of glucose. If, however, concentrated sulphuric or hydrochloric acids are allowed to come into contact with cellulose for only a short time at ordinary temperatures, another effect, known as "*parchmenting*" results. Paper, cotton fabrics, and the like swell on the surface when treated in this way, and this partly attacked and hydrolysed cellulose, endows the paper or the cotton fabrics after drying with a kind of finish and increased toughness.

Cellulose which has been partially broken down by the action of acids, and has been weakened, is called "*hydrocellulose*", and that which has been attacked by oxidizing agents is called "*oxycellulose*". Neither hydro- nor oxycellulose are homogeneous substances, but consist of mixtures of unchanged cellulose and decomposition products. They play a part in injuries to tissues.

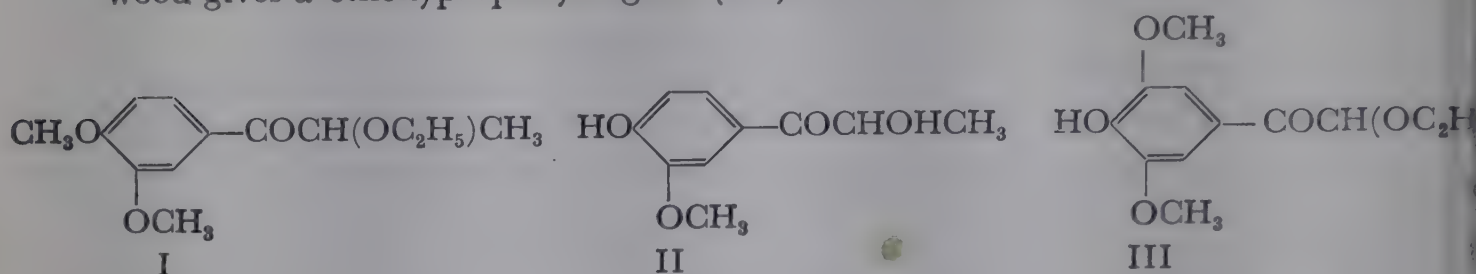
Cellulose fibres also suffer a change when acted upon by cold, concentrated alkalis. They take up the alkali and wrinkle strongly together. On washing with water the sodium hydroxide can be completely washed out again, but the cellulose retains a certain lustre, and an enhanced power of taking up dyes and moisture. The process was invented by Mercer for the pre-treatment of the fibre before dyeing and is named after him "*mercerization*". It is of practical importance. The cause of the mercerizing effect is not yet clear. It seems that the differences between native and mercerized cellulose depend on physical or crystallographic changes. Their X-ray diagrams are different.

Wood.¹ Lignin. Wood consists predominantly of cellulose, which may amount to two-thirds of the weight of the dried substance. In the wood of angiosperms there are in addition 1–2 per cent of *xylan* (wood gum) and up to 30 per cent of *lignin* [the wood of gymnosperms contains chiefly mannan in place of *xylan* (Bertrand)]. Whilst *xylan* belongs to the complex polysaccharides which do not resemble sugars, and can be decomposed by acids into xylose (and about 6 per cent of arabinose), the nature of lignin, and whether it is a homogeneous substance, is not yet clear. It is insoluble in most of the usual solvents. It is amorphous, possesses a considerable methoxyl content, and gives a number of colour reactions. It gives a deep cherry-red colour with hydrochloric acid and phloroglucinol, and a yellow colour with aniline sulphate. When *spruce wood lignin* is fused with caustic potash, protocatechuic acid is formed; on distillation with zinc dust small amounts of guaiacol and *n*-propylguaiacol (1-propyl-3-methoxy-4-hydroxybenzene) are among the products obtained; controlled

¹ CARL GUSTAV SCHWALBE, *Die Chemie der Cellulose*, 2nd ed. I. *Die Chemie der Hölzer*, Berlin, (1938). — H. D. TIEMANN, *Wood Technology: Constitution, Properties and Use*, New York, (1942). — LOVIS E. WISE, *Wood Chemistry*, New York, (1944).

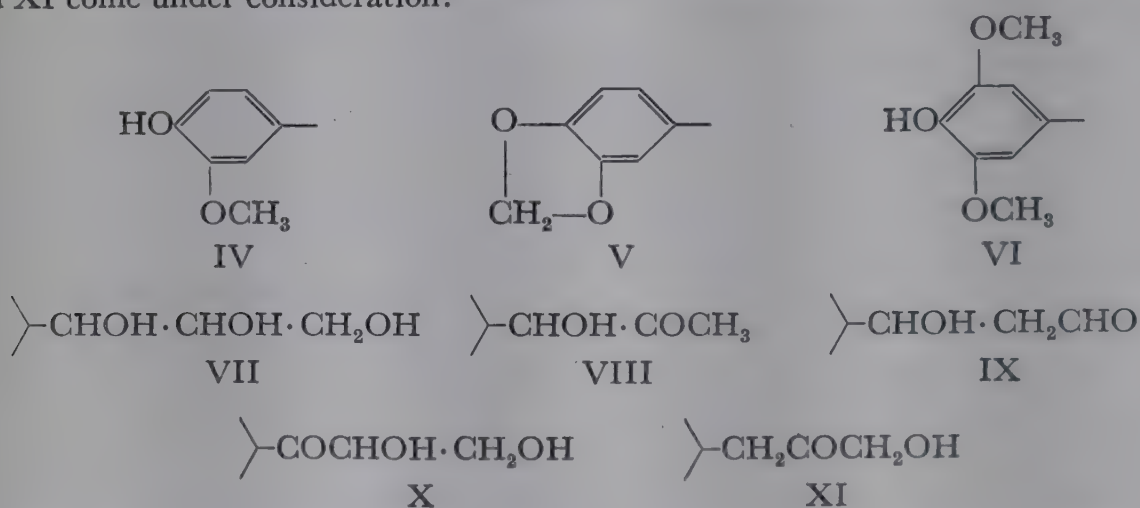
oxidation (with nitrobenzene) gives up to 25% vanillin. Fusion of *beech wood lignin* with caustic potash gave gallic acid in addition to protocatechuic acid, and also vanillin and syringic aldehyde, i.e. derivatives of pyrocatechol and pyrogallol.

Further degradation products of lignin have been obtained by extracting the wood with alcohol-hydrochloric acid (Hibbert). Taking spruce wood as a starting point, methylation of the extracted phenolic substances yields α -ethoxypropioveratrone (I), which probably arises from II. Under analogous conditions, maple wood gives α -ethoxypropiosyringone (III):



In addition, vanilloyl methyl ketone, the diketone corresponding to the ketoalcohol II, and similar compounds have been isolated.

According to Freudenberg and Hibbert, lignin is built up from phenylpropane derivatives of the guaiacyl type (IV), the piperonyl type (V) and the syringyl type (VI). For the side chains connected with the benzene nuclei the structures VII, VIII, IX, X, and XI come under consideration:



To obtain cellulose from wood, a process carried out on a large scale for the manufacture of paper and artificial silk, the lignin must be separated from the cellulose. This is done, for example, by boiling the wood (as pulp) with caustic soda under pressure, when the lignin dissolves, and pentosan (xylan) is destroyed. The cellulose, "sodium cellulose", remains unchanged. Another method is the "sulphite process". The small pieces of wood are submitted to long boiling with calcium bisulphite solution. This dissolves lignin and other non-cellulosic constituents of wood, but leaves the cellulose unattacked. Cellulose prepared in this way is mostly used for the manufacture of paper. Alcohol is prepared from the very large quantities of waste sulphite solution, which contains much sugar, or the sulphite solution is concentrated and the residue used as pitch, tar, and resin¹.

Lichenin (reserve cellulose). In many lichens, e.g. Iceland moss (*Cetraria islandica*), bearded lichen (*Usnea barbata*), *Evernia vulpina*, and in smaller

¹ See E. HÄGGLUND, *Die Sulfitablauge und ihre Verarbeitung auf Alkohol*, 2nd ed., Brunswick, (1921). — G. S. WITHAM, SR., *Modern Pulp and Paper Making*, New York, (1920). — HANS VOGEL, *Sulfitablauge und ihre Verwendung*, Stuttgart, (1939).

quantities in higher plants, there occurs a carbohydrate in the cell walls, or as a reserve substance, which is known as "lichenin", or reserve cellulose, and which shows great similarities to true skeletal cellulose, and especially to "hydrocellulose". Thus, total hydrolysis breaks it down to glucose; partial hydrolysis by means of acetic anhydride and sulphuric acid (acetolysis) converts, it like cellulose, into cellobiose. An essential difference between skeletal cellulose and reserve cellulose is that the latter is much more easily attacked and converted into sugars by enzymes, the so-called "lichenases", which are widely spread in plants and in invertebrate animals. Whilst the natural mixture of enzymes converts it into glucose, by the use of a partial enzyme, a trisaccharide has been isolated from the carbohydrate.

Lichenin dissolves in boiling water giving a colloidal solution. It is only slightly soluble in cold water. On acetylation, methylation, etc., it behaves similarly to true cellulose.

Hemicelluloses. This group comprises a series of complex polysaccharides which, like the above-mentioned lichenin, occur as constituents of the cell walls, and at the same time serve as reserve substances, i.e. they become occasionally reconverted into sugar by the plant. Many of them give on hydrolysis mannose and galactose in addition to glucose; they are therefore known as *mannans*, *galactans*, etc. Whether all these substances are homogeneous compounds is very doubtful. They usually dissolve in water with difficulty or not at all, and do not reduce. Certain enzymes found in plants and in the gastro-intestinal tract of invertebrates (e.g. snails), convert them into sugars. Mannans are found particularly frequently in seed cases, e.g. those of *Phytelephas*, the ivory-nut. Carob beans are also rich in mannans.

G. Bertrand has isolated a tetramannoside, $C_{24}H_{42}O_{21}$, and a pentamannoside, $C_{30}H_{52}O_{26}$, from ivory-nut mannan, F. Klages a mannobiose. Methylated ivory-nut mannan gives on hydrolysis, 2:3:6 trimethylmannose.

Artificial silk.¹ The importance attaching to artificial silk in recent times justifies the inclusion of a short description here.

All artificial silk is a transformation product of native cellulose. The principle of the manufacture of artificial silk is that cellulose, or cellulose derivatives, are brought into solution, and this solution is pressed through fine holes, so-called spinning nozzles, into a suitable precipitating agent, whereby the cellulose (or derivative) is rapidly coagulated or precipitated in the form of a fine thread. There are four different kinds of artificial silk in commerce:

(a) CHARDONNET RAYON (NITROCELLULOSE RAYON). This is obtained from cellulose nitrates (see p. 354) which have a medium nitrogen content, and which are therefore soluble in mixtures of alcohol and ether (collodion wool). The alcohol-ether solution of the cellulose nitrate is pressed through spinning nozzles either into air (dry spinning process) or into water (wet process). In the first case

¹ R. MORTGAT, *La fabrication de la soie artificielle par le procédé viscosé*, Paris, (L'édition textile). — A. CHAPLET, *Les Soies Artificielles*, Paris, (1926). — THOMAS WOODHOUSE, *Artificial silk or rayon, its manufacture and uses*, 2nd. ed., London, (1929). — V. HOTTENROTH, *Die Kunstseide*, 2nd ed., Leipzig, (1930). — M. H. AVRAM, *The rayon industry*, 2nd. ed., London, (1930). — A. LINDER, *Kunstseide*, 2nd. ed., Basel, (1930). — O. FAUST, *Kunstseide*, 4th and 5th ed., Dresden and Leipzig, (1931). — FRITZ OHL, *Die Kunstseiden. Nitrat-, Acetat-, Äther-, Viscose- und Kupferkunstseide*, Leipzig, (1931). — *Kunstseide*, ed. by ALBRECHT ANKE, Berlin, (1933). — PAUL AUGUST KOCH, *Kunstseiden und Zellwollen, ihre Herstellung, Eigenschaften und Prüfung*, Munich, (1938). — WILLI SIEGLE, *Die Kunstfaser. Wie werden Kunstseide und Zellwolle hergestellt und verarbeitet*, Stuttgart, 1938. — HELLMUT GUSTAV BODENBENDER, *Zellwolle, Kunstspinnfasern: Vistra, Flox, Cuprama*, 3rd ed., Berlin, (1939).

the solvent rapidly evaporates, and in the second it is withdrawn by the water. A thread of cellulose nitrate is formed. This is not yet suitable for the production of artificial silk owing to its ready inflammability. It must first be denitrated, which is done by treatment with sodium hydrogen sulphide, NaSH , or ammonium hydrogen sulphide, NH_4SH . This reduces the nitro-groups and eliminates them. Chardonnet rayon therefore consists of a regenerated, precipitated cellulose.

(b) **CUPRAMMONIUM RAYON.** In this process cellulose is dissolved in cuprammonium hydroxide, $[\text{Cu}(\text{NH}_3)_4](\text{OH})_2$ (Schweizer's reagent), and the solution forced through spinning nozzles into an acid bath, containing sulphuric acid, or acid salts. The cuprammonium hydroxide being neutralized, the cellulose is precipitated in the form of a thread.

(c) **VISCOSE RAYON.** Cellulose xanthate is prepared as described on p. 364-5. The "aged", viscous solution is forced through nozzles into the precipitating bath, which may contain either sulphuric acid or salts (sulphates, bisulphates, etc.). Usually the precipitated thread still consists of cellulose xanthate and this is converted into cellulose during the further treatment, e.g. by winding the thread on to spools in a sulphuric acid bath.

(d) **ACETATE RAYON.** This, the newest form of artificial silk, is obtained from cellulose acetates, the solution of which in organic solvents (chloroform, acetone) is passed through spinning nozzles into a precipitating bath. The thread of acetate rayon retains its acetyl groups, and therefore consists, not of regenerated cellulose, as in the case of the other three kinds of artificial silk, but of one of its esters.

The artificial silks possess a high lustre and suppleness, properties which make them similar to natural silk, and give to them the name. Chemically they are quite different from natural silk, which belongs to the proteins. Their disadvantages compared with natural silk are their lesser strength and durability, and their greater sensitivity towards damp air and water. On the other hand they are considerably cheaper than natural silk. The most resistant of the artificial fibres is acetate rayon.

Chardonnet, cuprammonium, and viscose rayon are to be considered chemically as regenerated, precipitated celluloses, in which, however, the chemical processes through which they have passed have left some traces. They show signs of slight degradation, have a somewhat greater reducing power, are more hygroscopic, and have an increased power of taking up dyes. Some of these properties can be traced in part to a change in the physical structure of artificial silk compared with the native cellulose fibres. The smallest cellulose particles, the cellulose micelles or crystallites, are no longer oriented all parallel to the fibre axis as in the native cellulose fibres, but in artificial silk are more or less disordered. There is, therefore, a loosening of the micellar texture and an increase in the active surface, with which is connected the increased capacity of the artificial thread for the adsorption of water and dyes, as well as its smaller mechanical and chemical stability. It should also be specially noted that the artificial and natural cellulose threads behave very differently towards enzymes. Whilst artificial silk threads are comparatively easily and completely converted into sugars by "cellulases" which occur in snails and other invertebrates, the breakdown of native cellulose (cotton) proceeds much slower.

Staple rayon. Among the modern artificial fibres, the so-called staple rayon has also acquired great importance. It is prepared from the same cellulose compounds as the

artificial silks, i.e. from viscose, from cellulose in cuprammonium solution, and from cellulose acetates. Whilst, however, in the manufacture of artificial silks a filament is produced in the way described above, which can be used directly for weaving and knitting, in the case of staple rayon the thread is cut into short lengths. The latter (after purification and bleaching) are then made into yarn by a spinning process. These artificial fibres are frequently subjected to a curling process. The spinning of the short artificial cellulose threads into yarn corresponds to the manufacture of woollen or cotton yarns from the respective natural fibres.

PART II.

CARBOCYCLIC COMPOUNDS

A. Aromatic compounds

CHAPTER 22

INTRODUCTION. CONSTITUTION OF BENZENE

The term "*aromatic compounds*" was originally applied without any sharp definition to different "aromatically"-smelling substances, which could be obtained from natural products (resins, balsams, etc.). Very soon, however, the name lost this meaning; aromatic chemistry became the chemistry of benzene in the widest sense, and to-day it covers in addition to benzene all carbocyclic compounds which are more or less similar in character to benzene.

Up to the beginning of the second half of the last century very few aromatic substances were known. Amongst them were benzoic acid, phenol, aniline, benzene, salicylic acid, and anthranilic acid. In all of them the common radical C_6H_5 , the *phenyl radical*, was supposed to occur. This view has been proved correct as a result of later work.

The great period of development for aromatic chemistry came in the second half of the nineteenth century. With unparalleled rapidity one new class after another of aromatic compounds was discovered. Coal-tar proved a store-house of numerous benzene derivatives of different kinds, and the young aniline dye industry gave a new impetus to this branch of organic chemistry. For some years now there has been a slowing down of the development in this direction. Although aromatic chemistry still has many questions to be solved, it must be admitted that we possess a good deal of information about many properties of benzene compounds. In modern times the centre of interest has shifted more and more to natural substances, of which the majority are not aromatic.

The collection of benzene derivatives into a special branch of organic chemistry is justified on various grounds. Kekulé had already recognized that in benzene no simple chain arrangement of carbon atoms, such as is met with in aliphatic compounds, could represent the formula of the compound, but that here the C-atoms were linked "more closely" together; as will be seen later, the arrangement is cyclic.

Benzene and its derivatives also show certain differences in chemical properties from the aliphatic substances. Although these differences are seldom fundamental, and are usually more quantitative than qualitative in nature, their practical effect is often very different.

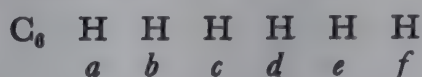
The ratio of carbon to hydrogen in benzene is 1 : 1, and the formula of the hydrocarbon is thus C_nH_n . It should, therefore, if we count on similar relationships as those which hold in the aliphatic series, be strongly unsaturated. Actually, however, benzene is a very stable substance, and although further investigation

shows it to possess unsaturated properties, these are nothing like so marked as in the case of the olefinic or acetylenic compounds. It is quite stable towards potassium permanganate in the cold, and bromine is not instantaneously added on to the molecule, as in the case of ethylene. Benzene thus undoubtedly possesses quite a different character from the unsaturated aliphatic hydrocarbons. To find an explanation of this in the structure of benzene will be one of our next tasks.

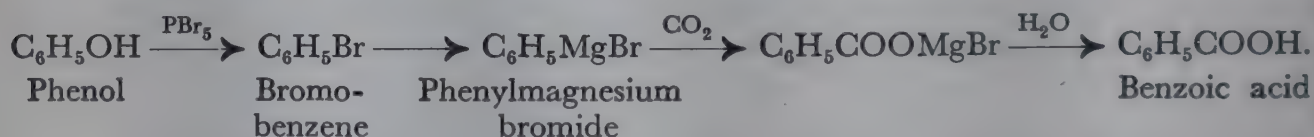
Constitution of benzene. The analysis of benzene gives the empirical formula C_1H_1 . Molecular weight determinations indicate that this simplest formula must be multiplied by six to give the molecular formula. Benzene thus has the molecular formula C_6H_6 .

Before it was possible to solve the problem of the structure of benzene it was necessary to discover whether all the six hydrogen atoms of benzene are equivalent, or whether they fulfil different functions. This question was answered particularly by Ladenburg (1874), and in part also by Hübner and Petermann. Their reasoning in its essentials will be followed in the proof given below:

Let the six benzene hydrogen atoms be represented by the symbols *a* to *f*.

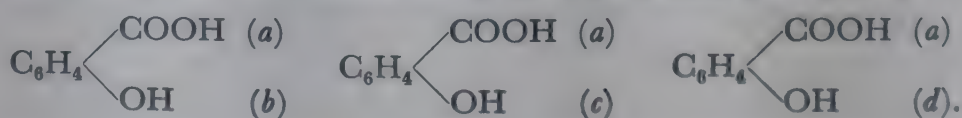


1. Suppose that in the monocarboxylic acid of benzene, *benzoic acid*, C_6H_5COOH , hydrogen atom *a* of the benzene nucleus is replaced by the carboxyl group. Then, the hydroxyl group in *phenol*, C_6H_5OH , must also be in position *a*, since the hydroxyl group can be readily replaced by the carboxyl group in a manner which can be easily followed, benzoic acid being formed:



2. There are three isomeric *hydroxybenzoic acids* (*salicylic acid*, *meta*-hydroxybenzoic acid, *para*-hydroxybenzoic acid). They all contain their carboxyl group in position *a*, since, if their hydroxyl groups are replaced by hydrogen, the three isomerides all give the same benzoic acid, of which the carboxyl group was supposed in (1) to be in the *a* position.

The hydroxyl groups in the three isomeric hydroxybenzoic acids must therefore occupy other positions, each of them having replaced a different hydrogen atom, as otherwise three different hydroxybenzoic acids could not exist. Let us assume that they have replaced the hydrogen atoms *b*, *c*, and *d*:

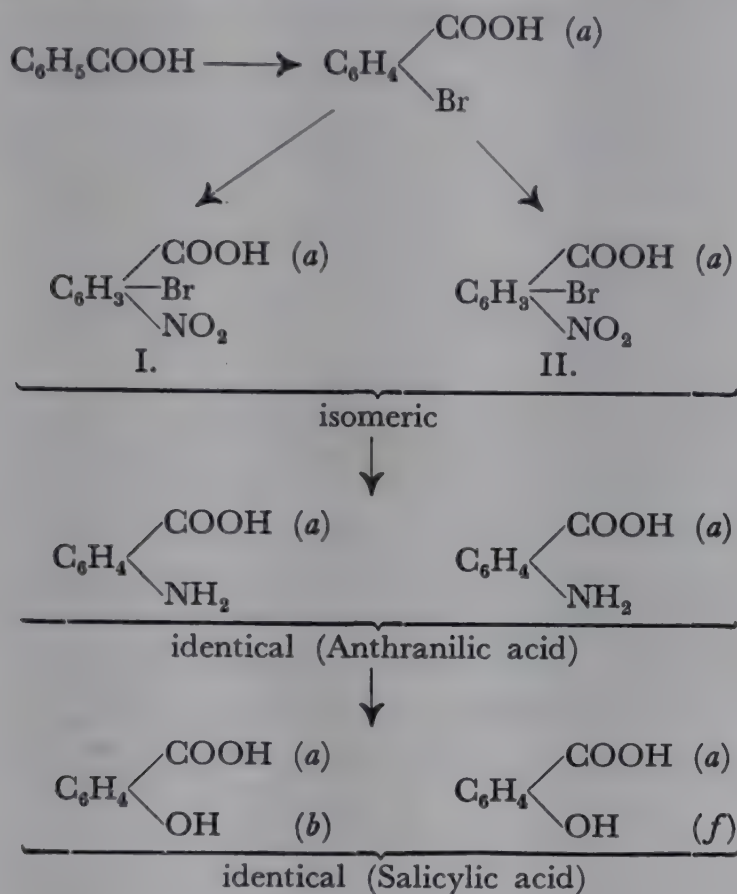


On distillation with lime all three hydroxybenzoic acids give the same phenol, with elimination of carbon dioxide, and it was shown in (1) that in this compound the hydroxyl group is in the *a* position. Hence it follows that the four hydrogen atoms of benzene designated by *a*, *b*, *c*, and *d*, are equivalent.

The hydrogen atoms *b*, *c*, and *d*, are not symmetrically placed with respect to *a*, as otherwise their replacement by hydroxyl, when the carboxyl group is in the *a* position, could not yield three different hydroxybenzoic acids. On the

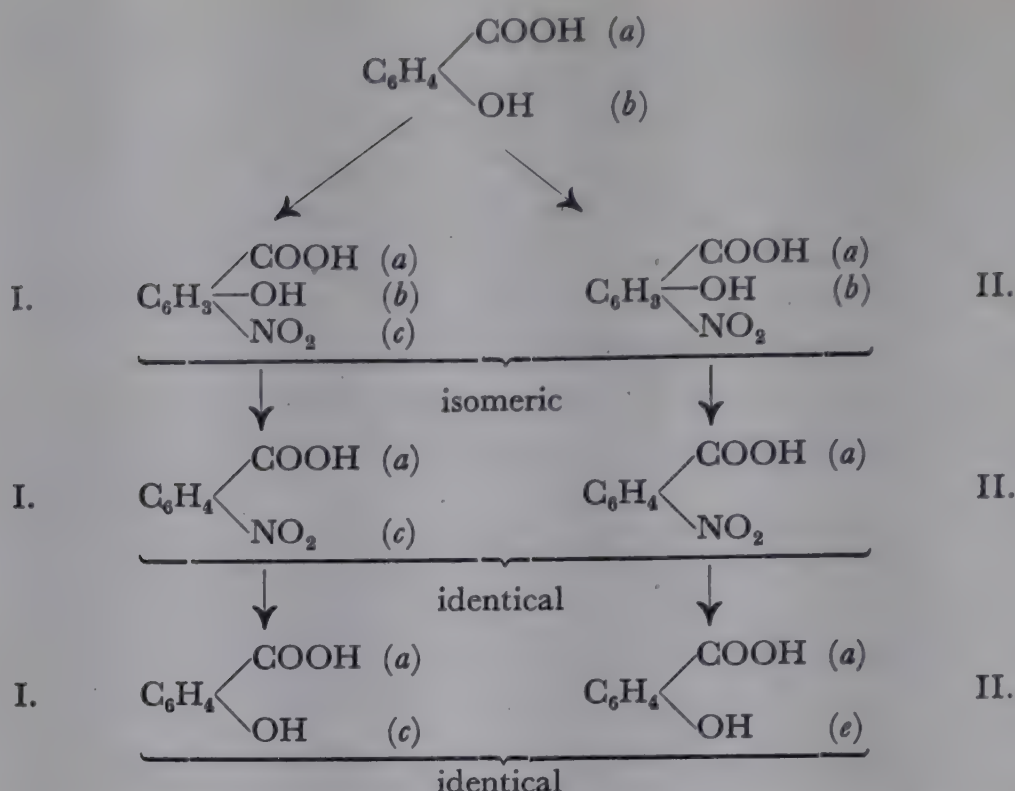
other hand, it can now be shown that there are two pairs of hydrogen atoms in benzene which are symmetrically placed with respect to *a*.

3. By the bromination of benzoic acid a *monobromobenzoic acid* (*meta*-bromobenzoic acid) is formed. If this is nitrated, two different but isomeric *nitrobromobenzoic acids* are formed. Both give the same aminobenzoic acid (anthranilic acid) on reduction. By replacing the amino-group by hydroxyl one of the above-mentioned hydroxybenzoic acids (salicylic acid), that in which the hydroxyl group was supposed to be in the *b*-position, is formed:



4. From these relationships it follows that the nitro-groups in the two *isomeric* nitrobromobenzoic acids, I and II, replace hydrogen atoms of benzene which stand in symmetrical positions with respect to the carboxyl in *a*. Since, as we saw, this is not the case for the hydrogen atoms *b*, *c*, and *d*, the nitro-group in one of the nitrobromobenzoic acids must occupy either place *e*, or place *f*. Suppose that it takes place *f*. We conclude that the position *f*, is equivalent to another, namely *b*. Since the positions *a*, *b*, *c*, and *d* have already been proved to be equivalent, the equivalence has now been proved to extend to five hydrogen atoms of the benzene molecule.

5. The following reactions give information on the nature of the sixth position in the benzene nucleus. We choose as our starting material the hydroxybenzoic acid which has the carboxyl group in position *a*, and the hydroxyl group in *b* (salicylic acid). On nitration, two isomeric *nitrohydroxybenzoic acids*, I and II, are obtained. By elimination of the hydroxyl groups, both are converted into identical nitrobenzoic acids, and by subsequent replacement of the NO_2 -groups by hydroxyl into *identical* hydroxybenzoic acids; the latter, however, are *different* from the hydroxybenzoic acid with the hydroxyl group in the *b* position, with which we started. The hydroxyl group must therefore be either in position *c* or *d*; it is in position *c*:



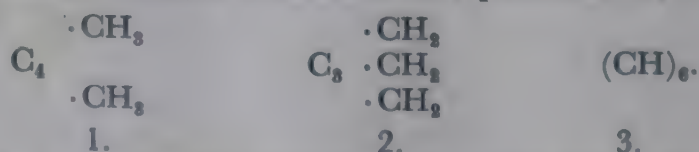
In nitrobenzoic acid I, the NO_2 -group is in the c position, as stated. This must also be true of the NO_2 -group in the nitrohydroxybenzoic acid I. The nitro-group in the isomeric nitrohydroxybenzoic acid II, must substitute the benzene hydrogen atom e , since the a position is already occupied with carboxyl, and the b position with hydroxyl, and the nitro-group cannot be in the c position, or the nitrohydroxybenzoic acids I and II would be identical. Position d cannot be considered for the nitro-group of nitrohydroxybenzoic acid II, because otherwise degradation to hydroxybenzoic acid II would give an acid with the OH -group in the d position, which, as we saw above, would not be identical with the hydroxybenzoic acid $\text{C}_6\text{H}_4 \begin{cases} \text{COOH (a)} \\ \text{OH (c)} \end{cases}$ (with OH in the c position).

Finally, the nitro-group of the nitrohydroxybenzoic acid cannot be in place f , since, according to the above, this position is symmetrical with b , with respect to a , and the hydroxybenzoic acid II would then be identical with the starting material, which is not the case.

It follows that in the nitrohydroxybenzoic acid II the nitro-group can only take up place e of the benzene molecule. It is symmetrical with c , with respect to a , as the identity of the nitrobenzoic acids I and II, and that of the hydroxybenzoic acids I and II proves. Hence it has been shown that all the hydrogen atoms of benzene, a, b, c, d, e , and f , are equivalent.

An immediate consequence of this fact is that *monosubstitution products of benzene can exist in only one form*. Experiment confirms this, as it has never been possible to prepare isomeric monosubstituted derivatives of benzene.

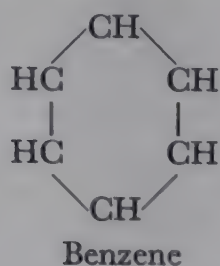
The arrangement of six *equivalent* hydrogen atoms to six carbon atoms, as required by the benzene formula, is limited to few possibilities, which are shown schematically below:



In the first case all the benzene hydrogen atoms are attached to two carbon

atoms, in the second to three, and in the last, they are distributed equally amongst all the carbon atoms. The isomerism existing in the benzene series, and particularly the fact that *disubstitution derivatives of benzene always exist in three isomeric forms*, can only be reconciled with the third of these formulæ. Formulæ 1 and 2 allow the possibility of only two isomeric disubstitution products.

The honour of putting forward, intuitively, a correct scheme for the linking of the six CH-groups from which benzene is constructed goes to Kekulé (1865). His hypothesis says that the six benzene carbon atoms are linked together in a closed six-membered ring; each of the carbon atoms is linked to one hydrogen atom:

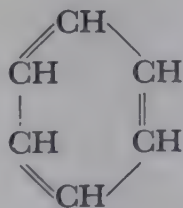


He was led to this view by the recognition that all simple aromatic compounds contain at least six carbon atoms, that they are comparatively richer in carbon than the corresponding analogues of the aliphatic series, and that the degradation products of complex aromatic substances very often possess six carbon atoms.

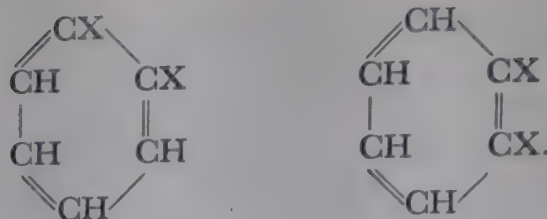
It was soon seen that Kekulé's benzene theory had created a sure foundation for aromatic chemistry, upon which this branch of chemistry could build almost without a failure. The larger the number of observations and the more accurate the knowledge of isomerism in the benzene series, the more clear it became that Kekulé's benzene formula was on the whole a correct expression of the structure of this hydrocarbon.

This does not mean that it does not leave certain questions unsolved. Particularly the affinity relationships in the benzene molecule and the spatial configuration of the molecule have later been much investigated, and even to-day these points are still debated.

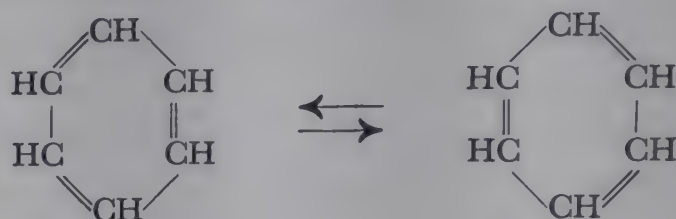
The simplest formula for benzene, which has been given above, contains carbon atoms which possess only three valencies. In order not to violate the theory of the constant tetravalency of carbon, which is thoroughly grounded on many facts, it is necessary to give some expression to the fourth valency of the benzene carbon atoms. Kekulé did this by introducing three double bonds into the benzene ring:



This is not quite satisfactory, however, for two reasons. Firstly, it does not explain why benzene is much more saturated in character than the olefins and polyolefins. Secondly, it would be expected that disubstitution products of benzene in which the substituting groups are *adjacent*, would exist in two isomeric forms, since the two substituents can be either attached to carbon atoms standing at the ends of a double bond, or at the ends of a single bond:



Actually, however, no more than *one* such disubstitution product has ever been found. This difficulty is avoided if, as has been done later, the double bonds in benzene are assumed to be not fixed but “oscillating”, as shown by the formulæ:



or if in benzene both of these structures occur simultaneously and in equal amounts. This “superposition” of different structures corresponds to the existence of different mesomeric states.

The following evidence speaks perhaps in favour of the “oscillating” double bonds. If *o*-xylene is oxidized, methylglyoxal, glyoxal, and diacetyl are found as degradation products. The first compound can only have been produced from an *o*-xylene of formula I, the last only from an *o*-xylene of formula II, whilst glyoxal could have been formed from either.

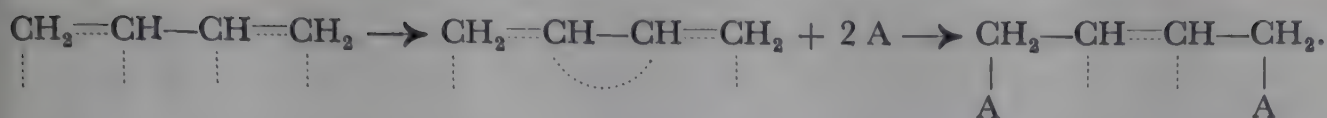


o-Xylene is thus a mixture of I and II, or the double bonds in benzene can change their positions (A. A. Levine and A. G. Cole). Later, Wibaut established that the three above-mentioned fission products of *o*-xylene are formed exactly in the ratio in which they must occur, if the two Kekulé benzene structures are present in equal amounts.

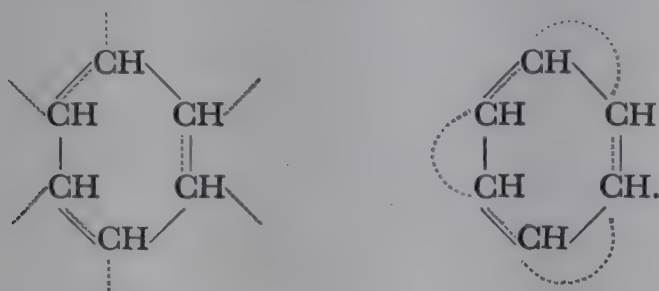
Other proposals for expressing the saturation of the fourth valency of the carbon atoms in benzene in the formula of the compound were made by Ladenburg (prism formula), Claus (diagonal formula), Armstrong and von Baeyer (centric formula), Dewar.



The formula put forward later by Thiele also seeks to explain the relatively saturated and stable behaviour of benzene, which distinguishes this compound so strikingly from the unsaturated hydrocarbons of the aliphatic series. It has been seen on p. 60 that addition takes place frequently at the *ends* of a conjugated system of double bonds. Thiele assumed therefore that the inner partial valencies in such a system were not effective as regards external addition, owing to mutual saturation:



If these considerations are applied to benzene, which may be regarded, according to Kekulé, as possessing three systems of conjugated double bonds, the saturation of the inner partial valencies makes a completely compensated molecule as regards its affinity relations. This would explain the stability and the relatively saturated character of the aromatic compounds:

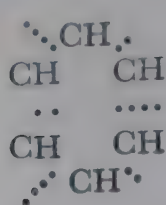


Thiele's theory, which proved very useful for the explanation of the special nature of benzene, cannot, however, as we shall see later, be generalized and applied to any given ring system. (Cf. the relationships with *cyclobutadiene* and *cyclooctatetraene*, Ch. 52 and 58). In common with the view of Claus (diagonal formula) and of Armstrong and Baeyer (centric formula), it endeavours to express the fact that the six CH-groups in benzene are united in an exactly equivalent manner, into a six-membered ring system of great stability by the total affinity of the valency forces at the disposal of the carbon atoms; the partial valency forces which are exerted by the molecule externally, and upon which thus depends the capacity for entering into addition reactions, are small, corresponding to the relatively saturated state of benzene, in any case smaller than in the olefin series. More recent work, moreover, has shown by an ever increasing number of examples that the differences in the degree of saturation of olefins and aromatic compounds are solely quantitative and are not fundamental, since, under suitable conditions very different groups can be added (hydrogen, halogens, ozone, hydrazoic acid, aliphatic diazo-compounds, etc.).

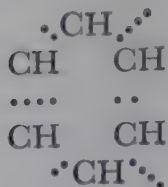
Finally, Kekulé's benzene formula, especially the form with "oscillating" double bonds (the so-called "oscillation formula") seeks to express this same idea in a somewhat different, but equally justified way. Kekulé's formula has found its way into more general use than the others, and is the one principally used at present.

The chemist always associates with it, as with the other benzene formulæ, a special degree of saturation, the so-called "aromatic" character.

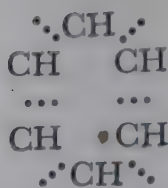
The modern electronic theory of valency and the electronic formulæ give the "single" and "double" bonds of the Kekulé benzene formula a real physical expression. The two Kekulé states of benzene can be expressed by these electronic formulæ in such a way that the six carbon atoms are alternately bound by one, and by two electron pairs (Figures I and II). These figures represent mesomeric forms, which are in a state of resonance. Both are completely equivalent and not distinguishable, which is in agreement with all the known facts of benzene chemistry.



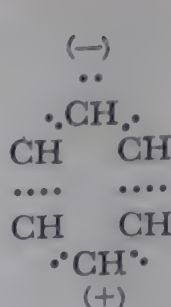
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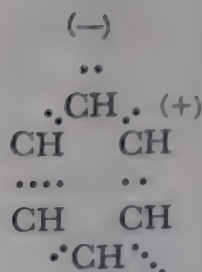
II



III



IV



V

Besides these two principal structures of benzene, in addition the electronic formulæ III, IV, and V can be discussed. In III, three electron pairs are "uncoupled" and distributed equally among the six carbon atoms. It has, moreover, to be borne in mind, that their total spin is zero and all the electrons compensate each other in pairs. This formula represents the Thiele structural formula in terms of the electronic theory. Finally, two further electromeric formulæ, IV and V, have been considered. These have a polar character and can be advantageously used as a basis for the theoretical treatment of several reactions of benzene.

The two Kekulé benzene structures (and to a certain extent also that of Thiele) may thus readily be expressed by means of the modern electronic formulæ. On the other hand, all the other earlier benzene formulæ which assumed affinity relationships between non-adjacent carbon atoms in the benzene ring have no physical sense and may, therefore, be excluded.

The mesomerism of benzene involves a considerable reduction of the free energy, and a decrease in the atomic distances. The latter are smaller (1.400 Å) than the distances between the carbon atoms in ethane (1.54 Å), and also somewhat smaller than the mean (1.46 Å) calculated from three single bonds (3×1.54 Å) and three double bonds (3×1.34 Å). Such contractions of atomic distances also occur in aliphatic resonance systems.

An indication of the considerable degree of saturation of benzene and its derivatives is the molecular refraction. In unsaturated aliphatic hydrocarbons with conjugated double bonds the molecular refraction shows an exaltation (see p. 66). In benzene, on the other hand, the molecular refraction corresponds to that calculated on the assumption of the existence of three ordinary double bonds. The very low heat of hydrogenation of benzene, too, is a sign of its low free energy; for the conversion of benzene into *cyclohexane* it is only 45 kg.-cal., whereas for the reduction of three C=C double bonds it is about 90 kg.-cal.

According to wave-mechanics a cyclic structure having, in addition to the electrons pair necessary to form *single* bonds between the C-atoms, *six* further electrons to link the C-atoms of the ring, represents a favoured grouping, poor in energy. We find this situation in compounds of "aromatic" character.

The *spatial arrangement* of the six benzene carbon atoms has been frequently and very thoroughly discussed. There are, at present, no chemical arguments against the assumption of a *planar* six-membered ring. On the contrary, a planar structure of the benzene molecule can readily explain all the observations of aromatic chemistry, and in particular the isomerism of benzene derivatives.

With a three-dimensional (e.g. octahedral) structure, substitution products of benzene would be expected to occur in stereoisomeric (e.g. enantiomorphic) forms, which so far have never been observed, except in those cases in which the

stereoisomerism is due to the special structure of side chains. The recently accomplished resolution of certain biphenyl derivatives into optically active components can also be explained without assuming a three-dimensional structure for the benzene nucleus (cf. p. 395 ff.).

The plane structure of the benzene molecule has been unequivocally proved by the X-ray analysis of hexamethylbenzene (Bragg, Lonsdale). The results obtained show that the six carbon atoms of the benzene ring lie in one plane and that the six alkyl groups radiate from the ring in the same plane. The distance between two *ortho* carbon atoms, as already mentioned, amounts to 1.40 Å, while those between the ring carbon atoms and the carbon atoms of the methyl side chains are 1.50 Å, i.e. of almost the same length as in aliphatic compounds.

Finally, the Raman spectra of benzene and its derivatives also speak in favour of a plane ring containing double bonds (Kohlrausch).

RAMAN SPECTRA. The data obtained from Raman spectra have within recent times become of considerable importance in the investigation of the internal structure of molecules.

If monochromatic light is allowed to fall on a transparent substance, e.g. a liquid, then the light corpuscles, or light quanta, will collide with the molecules of this substance. As a result, the light quantum transfers part of its energy to the substance, and its own energy suffers a corresponding change. Since the equation

$$\epsilon = h\nu$$

(ϵ = energy of the light quantum, ν = frequency, h = Planck's constant) must be obeyed, the frequency corresponding to the diminished energy of the light quantum will be smaller, i.e. the light will now appear in another place in the spectrum.

The change in energy which the light quantum undergoes as a result of its collision with the substance depends on the molecular structure of the substance. The energy taken up by the latter is used for the excitation of oscillations of the atoms within the molecule, the so-called nuclear vibrations. This excitation energy will therefore depend on the forces binding the atoms, the masses of the atoms, and their arrangement in space. The Raman spectrum produced by the impact of the light quanta on the molecules of the substance, i.e. the new lines observed in the spectrum, must therefore be characteristic for definite atomic linkages (C—C, C—H, N—H, O—H, C=O, etc.) and allow conclusions to be made concerning their nature and the spatial arrangement of the atoms. Analysis of the Raman spectrum may thus be useful in the elucidation of certain problems of constitution.

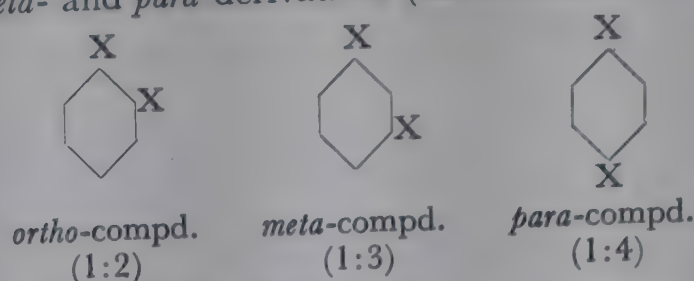
Substitution isomerism in the benzene series.¹ The justification of Kekulé's cyclic formula for benzene could not be better confirmed than by the agreement between the substitution isomerism predicted by theory and that found by experiment.

1. MONOSUBSTITUTION PRODUCTS of benzene invariably occur in only one form:

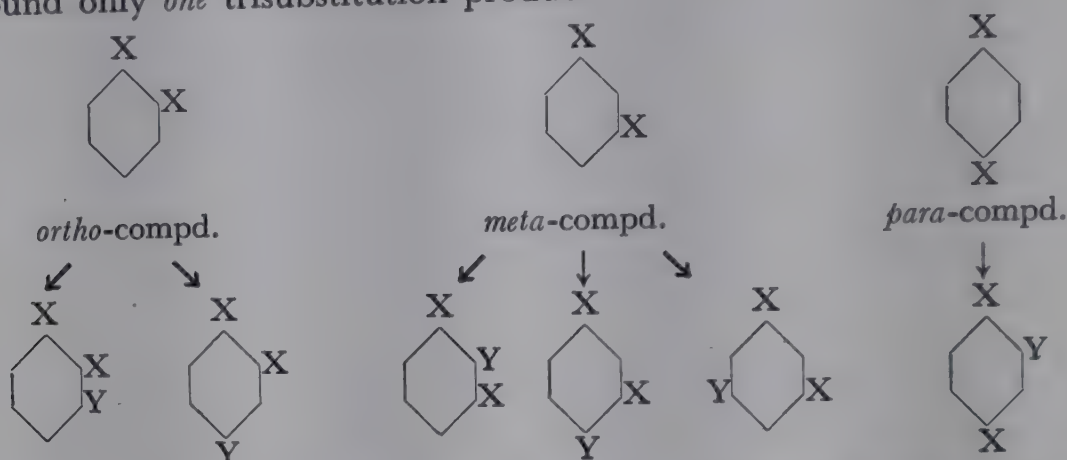


¹ See also table VI

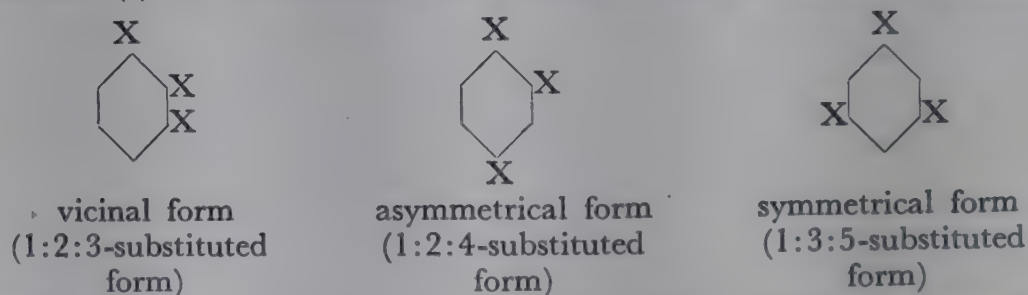
2. DISUBSTITUTION PRODUCTS of benzene exist in three isomeric forms, which are called *ortho*-, *meta*- and *para*-derivatives (abbreviated to *o*-, *m*-, *p*-):



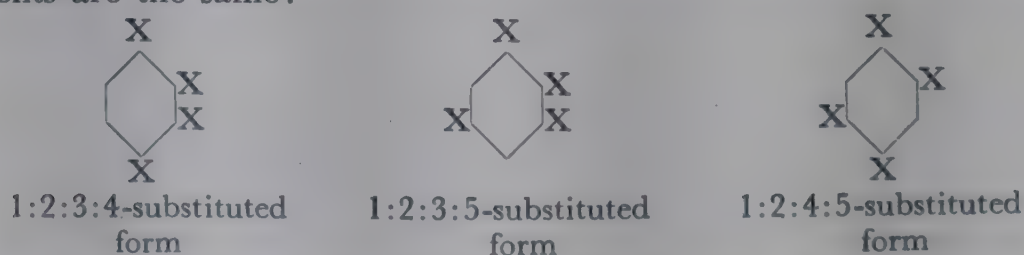
There are many methods of determining the relative positions of substituents in the nucleus, which can be varied from case to case. Many of these will be considered in later chapters. A general method consists in introducing into the disubstituted compound (with two identical substituents) a third substituent. An *ortho*-compound can give two, a *meta*-compound three isomerides, but a *para*-compound only *one* trisubstitution product:



3. There are three possible isomeric TRISUBSTITUTION COMPOUNDS of benzene if the substituents are all the same. They are known as *vicinal* (*vic*), *asymmetrical* (*as*), and *symmetrical* (*s*). If the substituents are different, the number of isomerides is greater:



4. TETRASUBSTITUTION PRODUCTS also exist in three isomeric forms if all the substituents are the same:



5. For PENTA- and HEXASUBSTITUTION DERIVATIVES, theory requires that there should be only one form of each if the substituents are all the same. Isomerides have never been found in such cases:



Section I

Compounds with a monovalent function

CHAPTER 23

AROMATIC HYDROCARBONS

Benzene

Benzene, the fundamental substance of aromatic chemistry, was discovered by Faraday in 1825 in a liquid produced by compressing oil-gas. It occurs in considerable quantities in coal-tar, in which its presence was first detected by A. W. Hofmann (1845), and from which it is now obtained technically.

The dry distillation of coal at temperatures of 1100–1300° gives, in addition to *coal-gas*, an aqueous liquid, *ammoniacal liquor*, and a viscous distillate, known as *coal-tar*. *Coke* remains in the retorts, and is used as a fuel and as a reducing agent for metal oxides in smelting.

Crude coal-gas contains hydrogen, methane, nitrogen, carbon monoxide and dioxide, cyanogen, hydrogen cyanide, higher saturated aliphatic hydrocarbons (especially ethane), ethylene, acetylene, benzene, naphthalene, hydrogen sulphide, ammonia, etc. The chief constituents are hydrogen and methane.

The *ammoniacal liquor* contains much ammonia, simple and cyclic amines, pyridine, hydrogen sulphide, thiocyanates, and other substances. It is an important source of ammonia.

In *coal-tar* about a hundred different substances have already been definitely detected, most of them being aromatic. Coal-tar is the outstanding source of aromatic compounds, and is the starting material for the aniline dye industry, and many other branches of industrial organic chemistry.

Its treatment begins with a fractional distillation. In order to avoid a very troublesome frothing it is necessary to separate the tar before distillation as completely as possible from *ammoniacal liquor*. Four fractions are then usually collected:

1. Light oil, which distils up to 170°.
2. Middle oil, boiling between 170 and 230°.
3. Heavy oil, boiling between 230° and 270°.
4. Anthracene oil, consisting of the fraction distilling up to about 340°, which is usually distilled *in vacuo*.

The residue left in the retorts is a viscous pitch, which is used in asphaltting streets, and for the manufacture of briquettes and varnishes.

Benzene and its homologues are the chief constituents of *light oil* (about 60–65 % of it). To isolate them, the liquid is carefully fractionally distilled. The distillates are washed with concentrated sulphuric acid to remove unsaturated, easily resinified hydrocarbons (hexene, cyclopentadiene, etc.), and bases, and after that, with alkali, to remove acid constituents, especially phenols. The fractions are then carefully redistilled, when *benzene* and *toluene* (methylbenzene) are obtained in a high state of purity. The higher boiling isomeric *xylene*s are not usually separated from one another. Very often their isolation is not attempted at

all, and their mixture with higher boiling fractions of light oil is used as a solvent under the name "solvent benzene", or "solvent naphtha".

The *middle oil* contains chiefly *naphthalene* and *phenols*, in addition to some of the constituents of light oil (benzene and its homologues) and some oils belonging to the heavy oil fraction. It is first rectified. The first fractions are rich in the benzene hydrocarbons and phenol. A considerable quantity of naphthalene crystallizes on cooling from the various distillates. It is separated by centrifuging, and is worked up for pure naphthalene by distillation or crystallization. The phenols, which are soluble in alkalis are extracted with sodium hydroxide solution, and reprecipitated by addition of acid.

Middle oil also contains considerable quantities of pyridine bases, and to obtain them the distillate, freed from phenols, is washed with sulphuric acid. The pyridine bases dissolve in the acid and can be separated again by the addition of alkalis. They are isolated and purified by distillation.

In *heavy oil*, the fraction of coal-tar distilling over between 230° and 270°, are found substances which are identical with the principal constituents of middle oil, especially naphthalene and phenol, as well as some which also occur in the higher-boiling anthracene fraction. A considerable amount of naphthalene crystallizes out when the oil cools. Amongst the phenols, heavy oil contains, in addition to the simplest phenol (carbolic acid), its homologues, viz. cresols, xylenols, etc. In addition it contains higher hydrocarbons, such as acenaphthene and biphenyl, and also bases, such as quinoline and *isoquinoline*. The residue of heavy oil remaining after removal of naphthalene and other constituents, is used for preserving wood.

Anthracene oil, the last distillate in the fractionation of coal-tar, solidifies on cooling to a soft crystalline mass, consisting chiefly of crystalline hydrocarbons. The chief constituent is anthracene (20–30 per cent). In addition it contains phenanthrene, acenaphthene, fluorene, the nitrogen compounds carbazole and acridine, etc., substances which are of outstanding importance in the dyeing industry. The oily residue separated from the crystals is used under the name "carbolineum" as a preservative for wood, and as a fuel oil.

The tar obtained by low-temperature carbonization of coal, known as "*low-temperature tar*", differs essentially in its composition from that of ordinary coal-tar referred to above. It contains few aromatic substances, and chiefly hydroaromatic and in part also aliphatic substances (pp. 43 and 57). It therefore follows that the majority of the aromatic compounds present in ordinary coal-tar are not contained as such in the coal itself, but are formed during the distillation by pyrolysis. Indeed it has often been shown (Berthelot, R. Meyer) that on passing aliphatic and hydroaromatic substances through red-hot tubes, that is, under the conditions which obtain in the distillation of coal, aromatic hydrocarbons and their derivatives are produced. Berthelot obtained in this way considerable quantities of benzene and naphthalene from methane, besides styrene from acetylene, and from a mixture of benzene and ethylene, passed through a red-hot tube, anthracene, naphthalene, styrene, etc. R. Meyer demonstrated the formation of benzene, toluene, naphthalene, anthracene, biphenyl, indene, fluorene, chrysene, and pyrene by the pyrogenic condensation of acetylene. These reactions give an idea of the origin of many of the constituents of coal-tar.

Benzene is a highly refracting liquid, boiling at 80.4°, and freezing at 4.5°. Its smell is aromatic, and not unpleasant. It is very slightly soluble in water, but

is miscible in all proportions with ether, ligroin, and various other organic solvents.

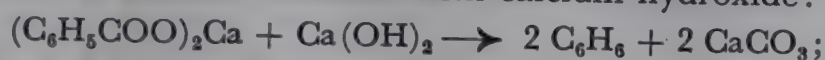
BENZENE from coal-tar is always accompanied by a sulphur-containing compound, *thiophen*, $\begin{array}{c} \text{CH}-\text{CH} \\ || \quad || \\ \text{CH} \quad \text{CH} \\ \diagdown \quad \diagup \\ \text{S} \end{array}$, which it is very difficult to remove. The presence

of this compound explains why crude benzene gives the *indophenin reaction*, which consists in the formation of a blue-green colour on adding isatin (see p. 568) and concentrated sulphuric acid to crude benzene. The fact that benzene obtained from benzoic acid did not give this reaction led to the discovery of thiophen by Victor Meyer. It occurs to the extent of up to 0.5 per cent in crude benzene. To separate benzene and thiophen use can be made of the fact that the latter is more easily sulphonated than benzene. Thus, if crude benzene is shaken with concentrated sulphuric acid, the thiophen dissolves more rapidly than the benzene.

For the commercial preparation of benzene the only processes which are of importance are the above-mentioned separation of the compound from coal-tar, and its preparation from coke-oven gas. There are, however, numerous *syntheses of benzene*. They can be considered under two headings; first the methods of obtaining it from aromatic compounds, and second, those in which aliphatic compounds are used as the starting substances.

(a) PREPARATION OF BENZENE FROM ITS DERIVATIVES:

1. Distillation of calcium benzoate with calcium hydroxide:



2. Hydrolysis of benzenesulphonic acid by boiling with hydrochloric acid:



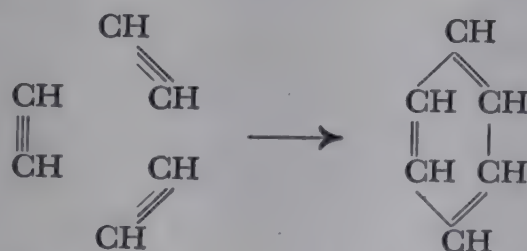
3. Distillation of phenol with zinc dust:



4. Preparation of benzene from aniline through the diazonium salts (see p. 478).

(b) FORMATION OF BENZENE FROM ALIPHATIC COMPOUNDS:

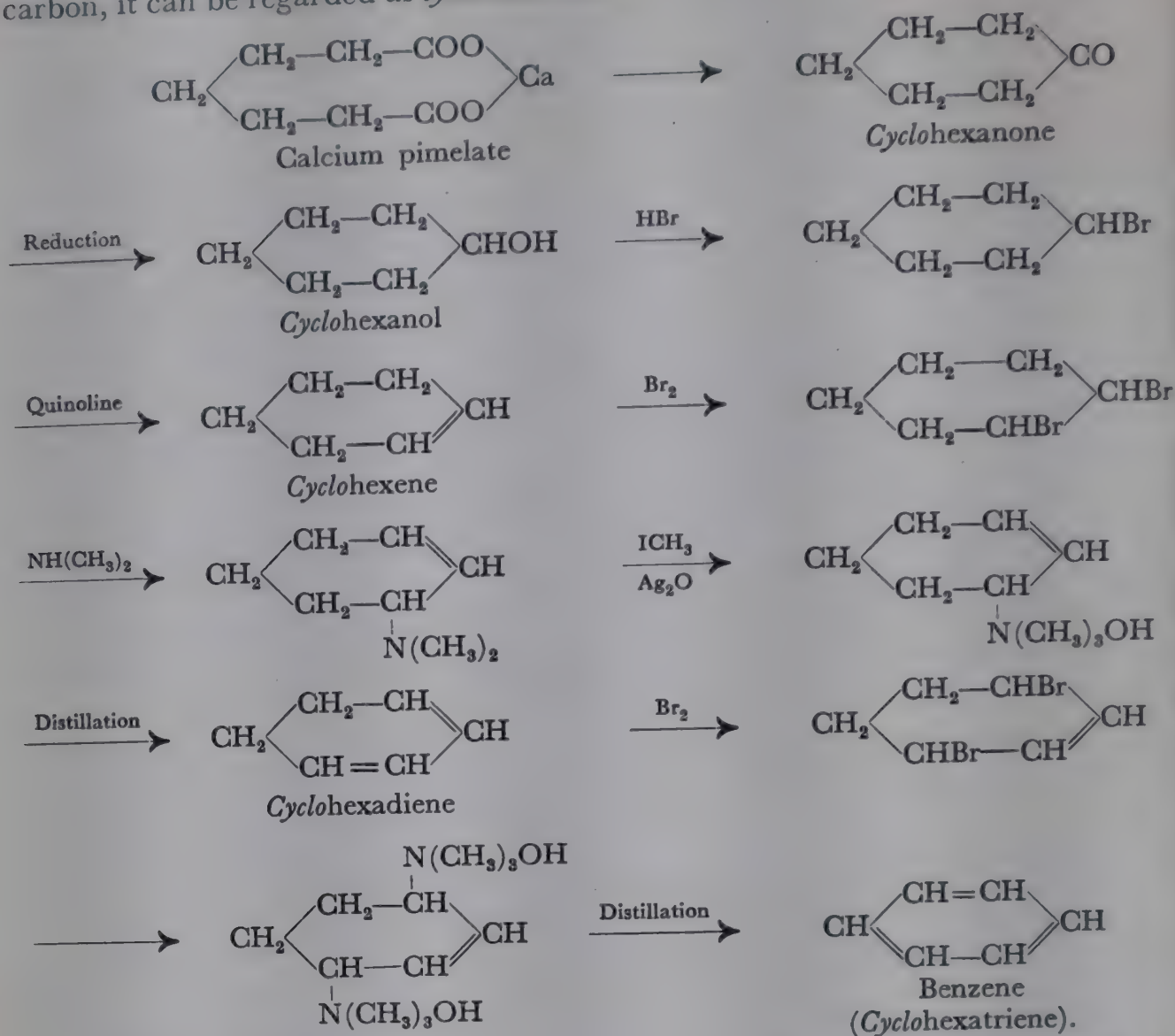
1. The synthesis of benzene due to Berthelot, consisting in passing acetylene through a red-hot tube, has been mentioned above. The reaction may be expressed by the following formulæ:



The yield of benzene can be increased by the use of catalysts (e.g. Al_4C_3 , and gas carbon).

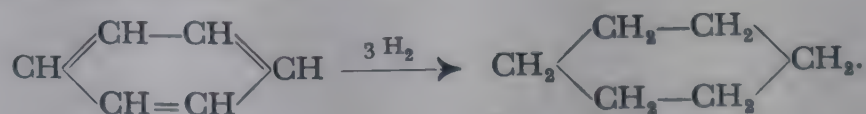
2. A synthesis of benzene due to Willstätter starts from pimelic acid. By dry distillation of its calcium salt it is converted in the known way into *cyclohexanone* (see Ch. 54). This is converted into *cyclohexanol* and then into *cyclohexene*, and the latter is dehydrogenated by Hofmann's method of exhaustive methylation, giving benzene. The synthesis provides a confirmation of the Kekulé formula for benzene, as the structural changes can be followed at each step. It

shows particularly that, in spite of the relatively saturated nature of the hydrocarbon, it can be regarded as *cyclohexatriene*:

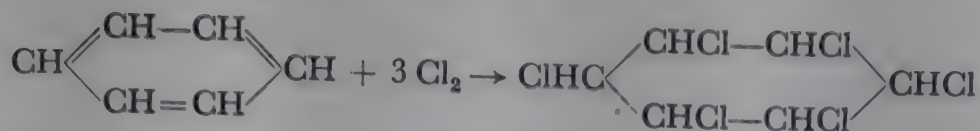


ADDITION REACTIONS OF BENZENE. The extraordinarily strong tendency to form addition compounds, which is a characteristic of unsaturated aliphatic hydrocarbons, is not so well marked in benzene, the differences being of a more gradual nature, though the addition of foreign atoms and groups to the benzene ring occurs quite frequently. The maximum number of monovalent groups that can be added is six.

An example of such addition to the benzene nucleus is the hydrogenation of benzene to give *cyclohexane*. This reaction proceeds quite smoothly if a catalyst, such as finely divided nickel, platinum, or palladium is present. Especially if the platinum metals are used, a very pure benzene, free from thiophen, must be employed if the reaction is to be successful:

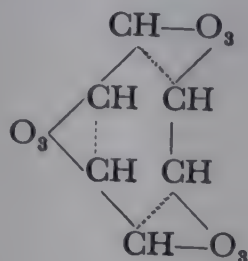


In sun-light, benzene also adds on chlorine and bromine. Of the *benzene hexachloride* (hexachlorocyclohexane) and *benzene hexabromide* respectively which are formed, the former is produced in several isomeric forms, which must be regarded, as in the case of the inositols (see Ch. 54), as *cis-trans* isomerides (different positions of the chlorine atoms on the two sides of the plane of the carbon ring):



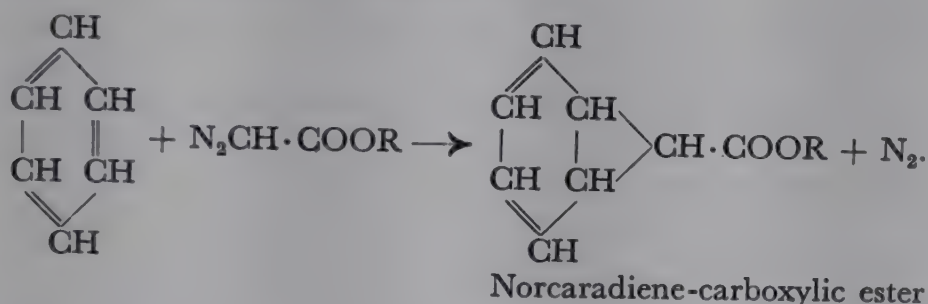
Up to now, four isomeric hexachlorocyclohexanes have been obtained in a pure state. They are designated as α - (m.p. 157.5–158°), β - (m.p. 309°), γ - (m.p. 112.5°), and δ - (m.p. 138–139°) forms. (An ϵ -isomer, observed in small quantities, is considered by some as a stereoisomer, and by others as a structural isomer). In particular, γ -hexachlorocyclohexane is a powerful insecticide, and is used to destroy insect pests on plants.

Ozone combines with benzene and its homologues forming *ozonides* (Harries). This reaction thus corresponds to that with members of the olefin series. Benzene ozonide:



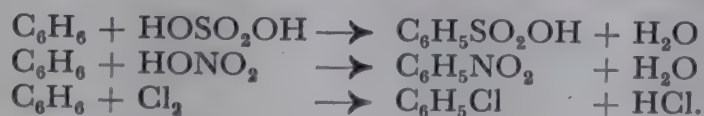
is very explosive and unstable.

A peculiar addition reaction shown by benzene, which will be more fully considered in a later chapter, is the addition of diazoacetic ester. A bicyclic compound, norcaradiene-carboxylic ester, or pseudo-phenylacetic ester (cf. Ch. 57), is formed with elimination of nitrogen:



Analogous reactions are known in the olefin series, so that also in this case benzene acts in fundamentally the same way as an unsaturated aliphatic compound, or an unsaturated hydroaromatic hydrocarbon.

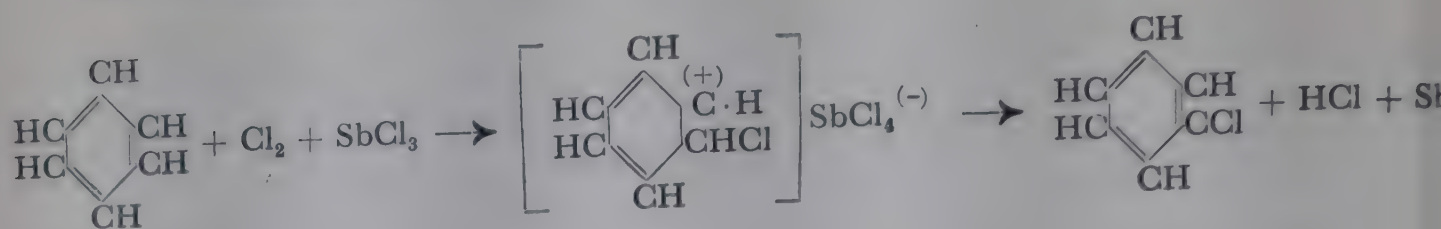
Benzene and its homologues, however, behave differently from the olefins, as regards sulphonation and nitration, and, under certain conditions, the action of halogens on them. Whilst ethylene *adds on* fuming sulphuric acid and halogens (see p. 53), concentrated sulphuric acid, concentrated nitric acid, and chlorine in the presence of certain catalysts, *substitute* in the benzene ring. The products of the reaction are benzenesulphonic acid, nitrobenzene, and chlorobenzene:



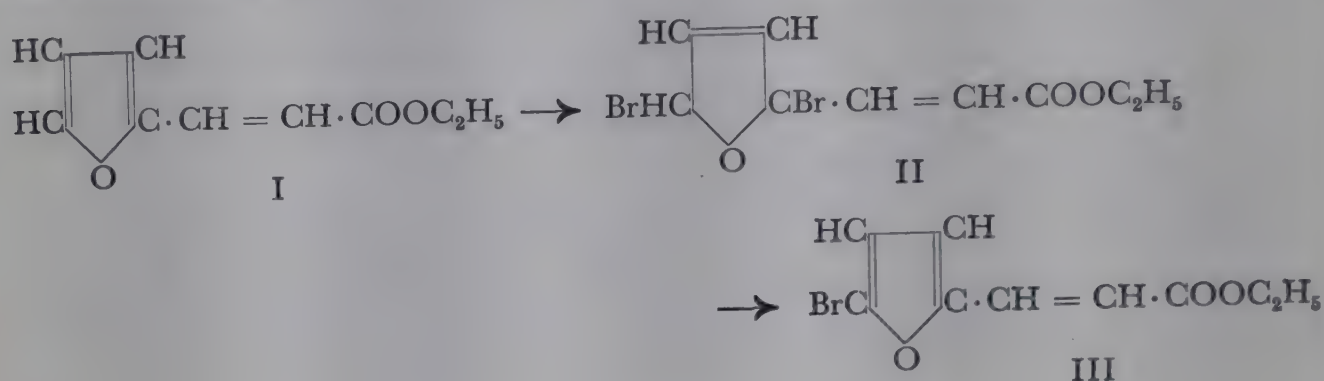
The mechanism of such substitution reactions is not the same in every case. According to the chemical nature of the compound undergoing substitution and the substituting agent, there is a variety in the types of reactions which take place in the first phase of the reaction.

In some cases, addition reactions appear to precede the substitution. This is, for instance, the case, according to P. Pfeiffer and Wizinger, when benzene and its derivatives are halogenated in the presence of halogen carriers (e.g. SbCl_3 , cf. p. 413). As intermediate products halogeno salts are here formed, in which a benzene carbon atom carries the

positive charge of the cation. The unstable halogeno salt decomposes to give the benzene derivative substituted in the nucleus by halogen:



Addition compounds of a different type appear to be the primary reaction products in the substitution of certain furan derivatives, similar in character to benzene. Thus, when β -(2-furyl)-acrylic ester (I) is brominated, the dibromo-addition product (II) is formed first, which then splits off HBr to give β -(5-bromo-2-furyl)-acrylic ester (III) (H. Gilman):



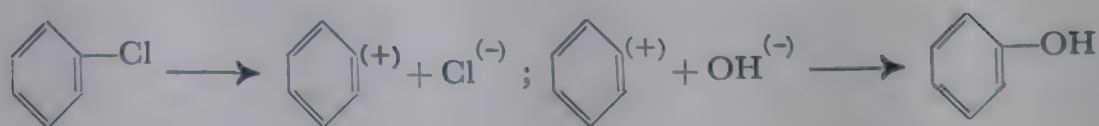
In many other cases, however, substitutions in the aromatic nucleus take place directly and no evidence for intermediate addition products can be found. Before the new substituent enters the benzene ring, the old one is detached. According to Ingold and other investigators, the detachment may take place in three different ways:

1. The leaving substituent takes *both* the bonding electrons with it, and is thus detached as an anion. In this case the entering substituent must also be an anion, i.e. it must bring along with it the electrons required for the linking. Here, the substituent approaches directly the atomic nucleus of the carbon atom. This type of substitution has therefore been called *nucleophilic* (nucleus-seeking) substitution. As an abbreviation for it the symbol S_N is used.

2. The leaving substituent does not take with it any of the electrons by which it had been linked to the C-atom. It is thus detached as a cation. Since the newly entering substituent (also a cation) finds the required bonding electrons already present, this type of substitution is called *electrophilic* substitution, which is abbreviated to S_E .

3. The leaving substituent takes one of the two bonding electrons with it and leaves the other behind. In this case it is detached as an atom or a radical, and it can therefore only be replaced in a similar way. This substitution is of the so-called "radical type", and is represented by the symbol S_R .

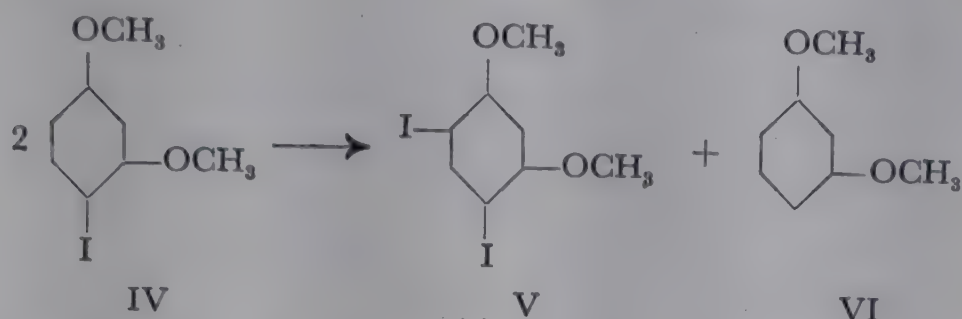
Nucleophilic substitutions occur especially frequently. This class includes, for example, the reactions of organic halogen compounds with bases, the halogen being replaced by OH. The substitution may take place either in steps:



or directly:



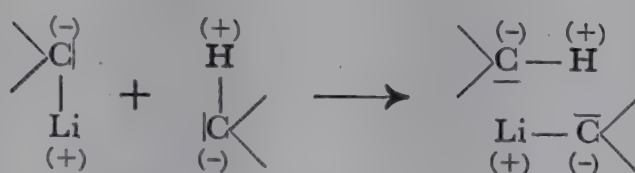
Several very interesting examples of electrophilic substitution have just recently been reported. In aromatic halogen compounds it has already previously been observed that the halogen atoms, linked to the aromatic nucleus, may wander, sometimes within the same molecule, and sometimes from one molecule to another. These migrations are favoured by catalysts, such as sulphuric acid, aluminium chloride, boron fluoride, etc. For example, 4-iodoresorcinol dimethyl ether (IV) is converted by the action of boron fluoride compounds very smoothly into 4:6-diiodoresorcinol dimethyl ether (V) and resorcinol dimethyl ether (VI):



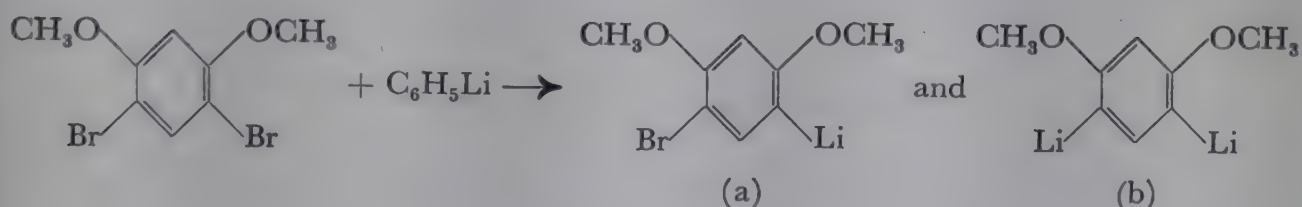
The mechanism of such reactions is, according to H. Meerwein, an electrophilic substitution, i.e. the halogen atom migrates as a cation, without the electron pair which had linked it to the carbon atom, and changes places with a hydrogen atom, also carrying a positive charge.

The reaction is reversible and is favoured by all those factors which tend to make the halogen-carrying carbon atom negatively charged, thus stabilizing its electron octet (e.g. by OH^- , OCH_3^- , NH_2^- groups).

Also the surprising replacement, discovered by G. Wittig, of hydrogen or halogens in organic compounds by lithium by the action of phenyllithium may be explained thus, that the lithium is detached from phenyllithium as a cation (i.e. leaving the two bonding electrons behind at the C-atom), and then replaces cationic hydrogen or cationic halogen in the benzene nucleus:



Thus, for example, from dibromoresorcinol dimethyl ether and phenyllithium the mono- and dilithium derivatives (a) and (b) are formed:

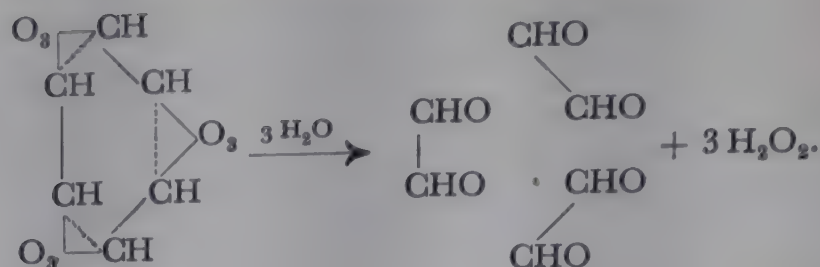


A combination of lithium and bromine to lithium bromide is not possible as both atoms are cationic.

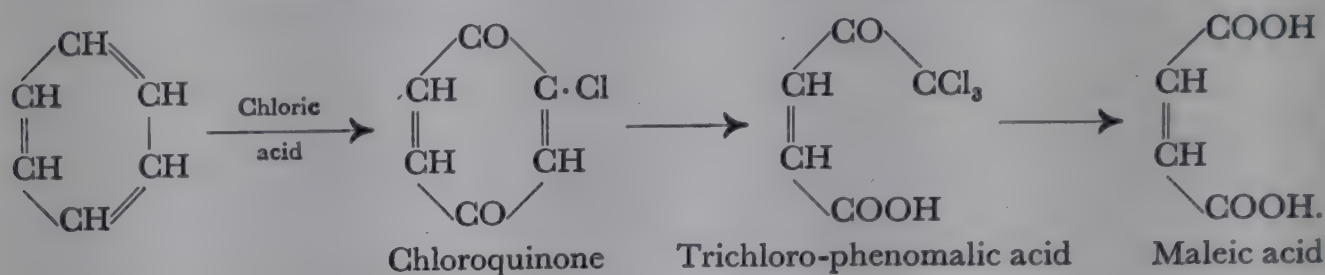
These few examples show the diversity in chemical substitution processes. They contribute considerably towards making aromatic chemistry more interesting and extensive.

RUPTURE OF THE BENZENE RING. The degradation of benzene to give aliphatic compounds may be brought about in several ways. Thus, if benzene is heated with hydriodic acid to a high temperature, some *normal hexane*, in addition to *cyclohexane* and *methylcyclopentane* (see Ch. 50), are formed.

Hydrolysis of benzene ozonide gives glyoxal:

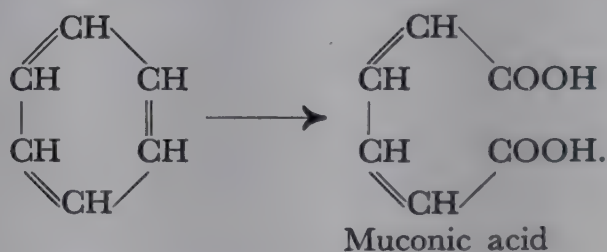


The unsubstituted benzene nucleus is quite stable towards *oxidizing agents*, though in special cases the ring may be ruptured by oxidation. By the action of chloric acid, the hydrocarbon is first converted into chloroquinone, which is then further oxidized to trichloro-phenomalic acid, and finally to maleic acid:



Benzene has also been oxidized to maleic acid by atmospheric oxygen, using vanadium pentoxide as a catalyst.

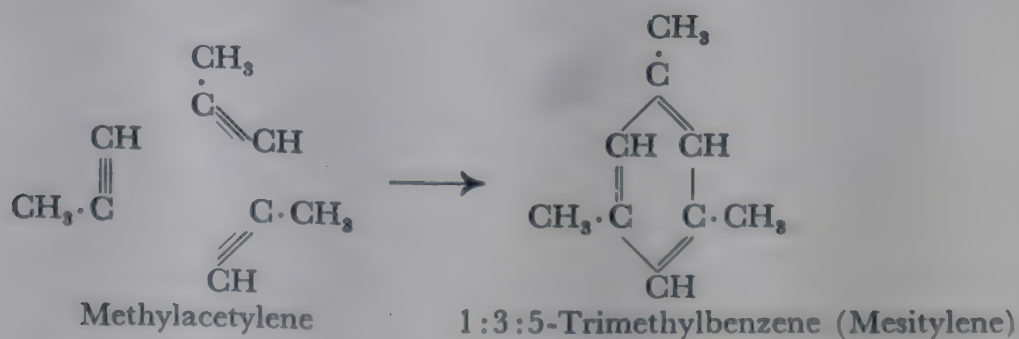
In the animal organism (dogs, rabbits) benzene is partly decomposed into *muconic acid* (*trans*-form, m.p. 298°). This simple and straightforward degradation of benzene to an aliphatic unsaturated dicarboxylic acid is of considerable physiological interest:



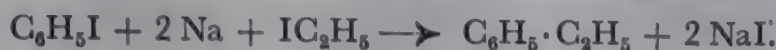
Up to the present it has not been possible to bring about this reaction *in vitro*, though it has been observed with a derivative of benzene, phenol, $\text{C}_6\text{H}_5\text{OH}$, when submitted to mild oxidation. Peracetic acid breaks down phenol to *cis-cis*-muconic acid (m.p. 187°). The presence of the OH-group in the benzene nucleus makes the latter more easily attacked.

Homologues of benzene

SYNTHESES. 1. Several alkyl homologues of benzene are produced by the polymerization of alkylated acetylenes. In most cases the condensation occurs more easily than with acetylene itself, and is effected, as in the latter case, by passing the substance through a red-hot tube:

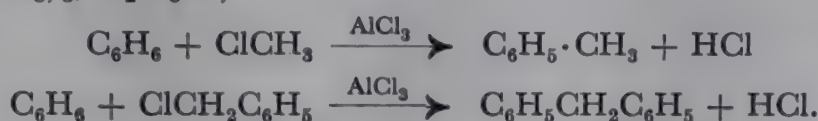


2. The Wurtz synthesis of hydrocarbons (p. 29) was applied by Fittig in 1864 to the synthesis of homologues of benzene. The reaction consists in the action of sodium on a mixture of an alkyl halide and an aryl halide. The presence of ethyl acetate assists the reaction, which may proceed through similar intermediate stages as in the the Wurtz synthesis of the paraffins (see p. 29):



Iodine and bromine compounds react more readily than the corresponding chlorine derivatives.

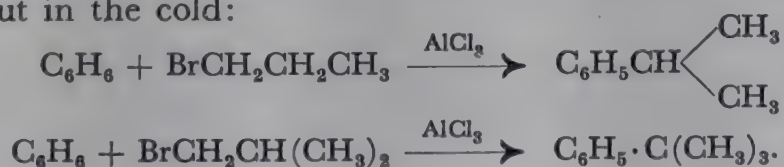
3. The Friedel-Crafts synthesis. This consists in the action of alkyl halides on benzene and other aromatic hydrocarbons in the presence of anhydrous aluminium chloride.¹ The latter takes part in the reaction and appears primarily to form ternary, reactive addition compounds with the alkyl halide and the hydrocarbon (J. F. Norris isolated, for instance, compounds of the type $\text{Al}_2\text{Br}_6 \cdot \text{C}_6\text{H}_3(\text{CH}_3)_3 \cdot \text{C}_2\text{H}_5\text{Br}$).



By means of the Friedel-Crafts reactions all benzene hydrogen atoms may be successively replaced by alkyl radicals. However, the reaction is not always straightforward; for the anhydrous aluminium chloride not only reacts as a synthesizing agent, but also has a decomposing action, and may partially break down side chains. Thus, in the treatment of the methyl homologues of benzene with aluminium chloride various stages in the decomposition occur simultaneously:



Another reason why this reaction does not always proceed in a straightforward fashion is that aluminium chloride may cause rearrangement of alkyl halides. Thus, if *primary* alkyl halides are used in the Friedel-Crafts reaction, derivatives of *secondary* or *tertiary* alkyl halides are often obtained, especially if the reaction is not carried out in the cold:



In spite of this, the method serves quite well for the synthesis of aromatic hydrocarbons with side chains.

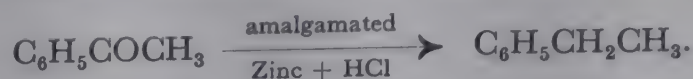
Sometimes the reaction between a halogen compound and an aromatic hydrocarbon can proceed without the presence of a catalyst, though a somewhat higher temperature has to be used. Thus, *p*-benzyl-biphenyl is obtained by boiling together benzyl chloride and biphenyl. Instead of AlCl_3 as a condensing agent in the alkylation of aromatic compounds with aliphatic halides, hydrogen fluoride has recently been recommended.

In place of the alkyl halides, olefins, such as ethylene or propylene, may also be used in the Friedel-Crafts reaction; when reacted with benzene and aluminium chloride they give rise to various ethylbenzenes. Boric esters, $(\text{C}_n\text{H}_{2n+1}\text{O})_3\text{B}$, also seem occasionally to be able to replace alkyl halides. Primary and secondary

¹ C. A. THOMAS, *Anhydrous Aluminium Chloride in Organic Chemistry*, New York, (1945).

alcohols also condense with aromatic hydrocarbons in the presence of aluminium chloride or boron trifluoride at high temperatures to give homologues of benzene, ethylenic compounds being possibly formed as intermediate products.

4. In many cases homologues of benzene may suitably be prepared by the reduction of mixed aromatic-aliphatic ketones with amalgamated zinc and concentrated hydrochloric acid (Clemmensen). The ketones themselves are conveniently obtained from aromatic hydrocarbons and acid chlorides by procedures to be described later:



5. In certain cases the reduction of aromatic chloromethyl derivatives, RCH_2Cl , has been recommended for the preparation of hydrocarbons (see p. 417).

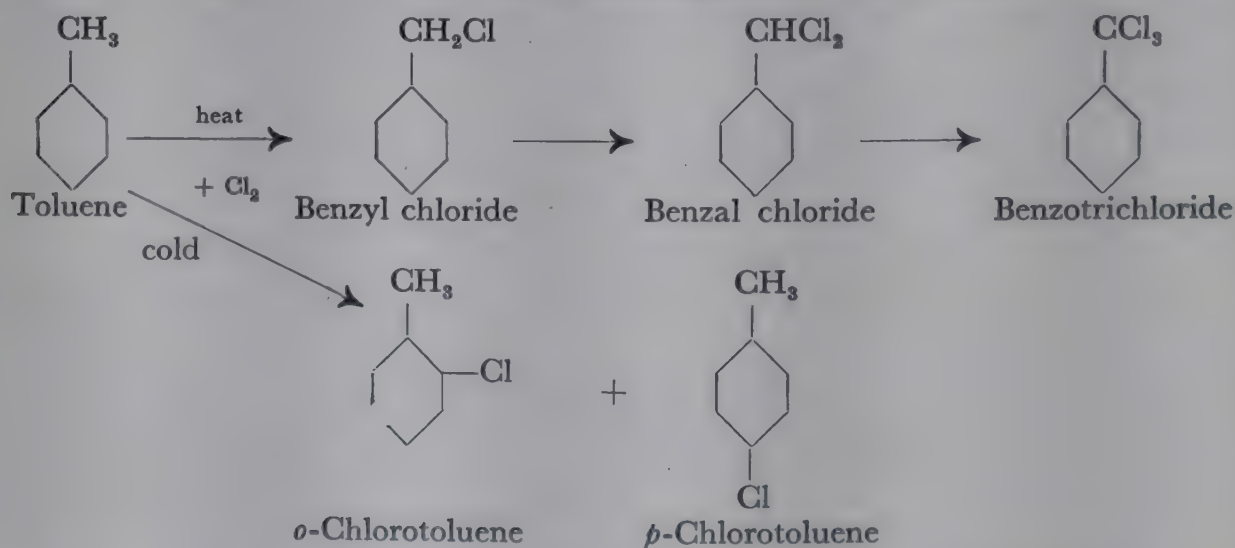
PROPERTIES OF THE HOMOLOGUES OF BENZENE. The lower alkyl homologues of benzene are very similar to benzene itself in physical and chemical properties. They are almost insoluble in water, and their smell is reminiscent of that of benzene.

The following table gives the boiling points of the first few members:

Benzene	C_6H_6	b.p. 80.4°	Hemimellitene	$\text{C}_6\text{H}_3(\text{CH}_3)_3$	b.p. 175°
Toluene	$\text{C}_6\text{H}_5\text{CH}_3$	b.p. 110°	Pseudocumene	$\text{C}_6\text{H}_3(\text{CH}_3)_3$	b.p. 169°
<i>o</i> -Xylene	$\text{C}_6\text{H}_4(\text{CH}_3)_2$	b.p. 142°	Mesitylene	$\text{C}_6\text{H}_3(\text{CH}_3)_3$	b.p. 165°
<i>m</i> -Xylene	$\text{C}_6\text{H}_4(\text{CH}_3)_2$	b.p. 139°	Ethylbenzene	$\text{C}_6\text{H}_5\text{C}_2\text{H}_5$	b.p. 136°
<i>p</i> -Xylene	$\text{C}_6\text{H}_4(\text{CH}_3)_2$	b.p. 138°	Propylbenzene	$\text{C}_6\text{H}_5\text{C}_3\text{H}_7$	b.p. 159°

The introduction of a new CH_3 -group raises the boiling point by about 30° on the average.

The alkyl homologues of benzene behave like benzene itself towards nitric and sulphuric acids. They are nitrated or sulphonated in the nucleus. Their reaction with chlorine can vary with the experimental conditions. Thus, at higher temperatures, chlorine successively replaces the hydrogen atoms of the side chain in toluene, but in the cold, the halogen enters the nucleus:



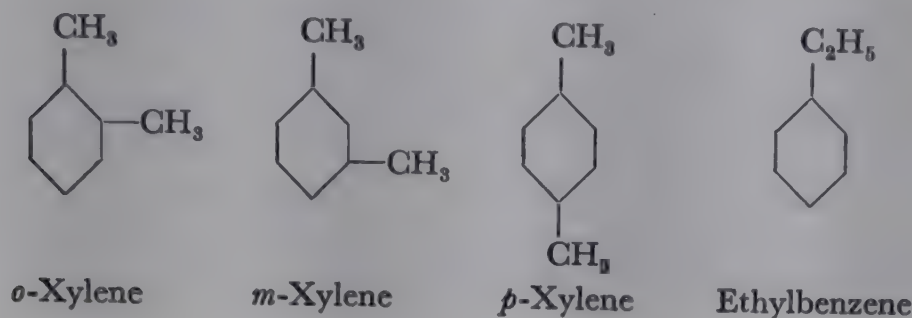
By treating the benzene homologues with potassium permanganate, the side chains are oxidized, and each one is converted into a carboxyl group. The reaction is therefore suitable for the determination of the number of side chains present in the hydrocarbon.

TOLUENE, , is found in coal-tar and in coke-oven gas, and is always obtained from these industrially. Its name is derived from tolu balsam,

from which it has been isolated. Coal-tar toluene has, like benzene, an impurity containing sulphur, from which it, too, can only be separated with difficulty. This is *thiotolen* (see Ch. 59), a methylthiophen. To detect the presence of thiotolen, a mixture of phenanthrenequinone and concentrated sulphuric acid is added to the impure toluene, when a blue colour results.

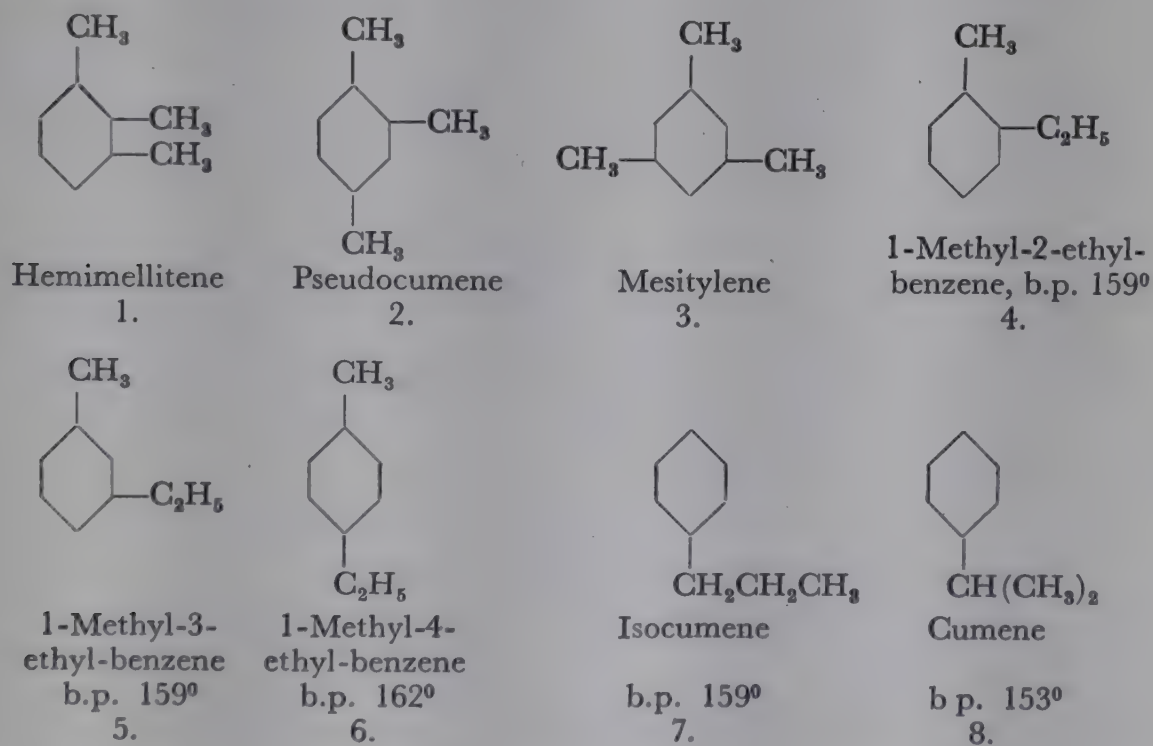
Toluene is important as a starting point for the preparation of dyes and explosives (trinitrotoluene), which will be met with again in later chapters.

HYDROCARBONS OF THE FORMULA C_8H_{10} . The three isomeric xylenes,



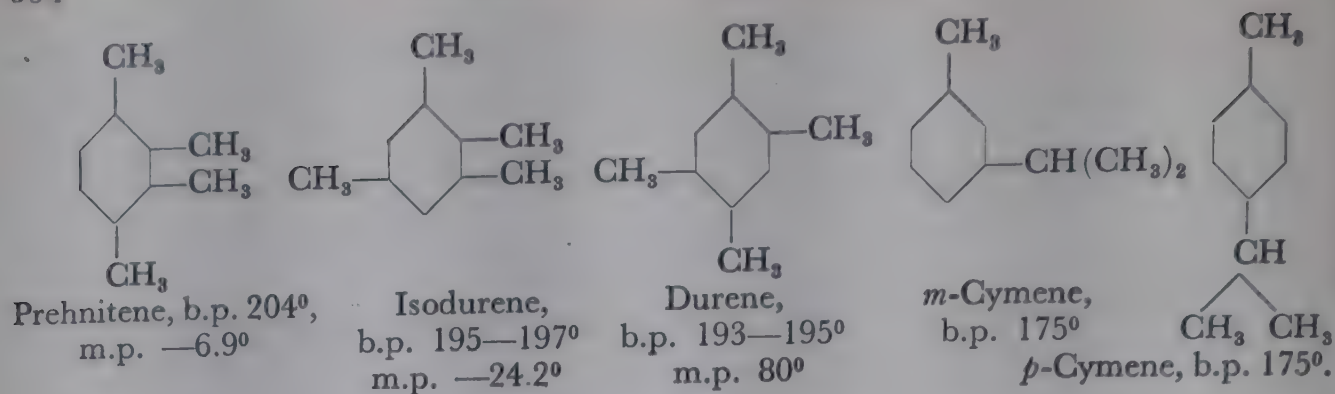
are contained in coal-tar. Their separation is difficult and is only possible by the use of special procedures. For this reason the mixture of isomerides is generally used for technical purposes. Their amino-derivatives are used in the manufacture of dyes, and the hydrocarbons themselves for the preparation of lacquers, and as solvents for rubber. *m*-Xylene is used in the preparation of "xylene musk" (see p. 421).

HYDROCARBONS OF THE FORMULA C_9H_{12} . There are eight possible isomerides, all of which are known:



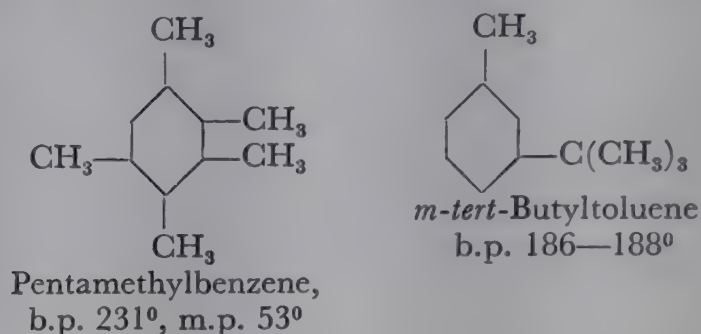
The three trimethylbenzenes are found in coal-tar. Mesitylene can also be readily obtained by synthesis. Cumene is a degradation product of various terpenes and camphors.

HYDROCARBONS OF THE FORMULA $C_{10}H_{14}$. Of the large number of possible isomerides (22), only the following will be mentioned:



Isodurene and durene are found in certain mineral oils. *m*-Cymene has been detected in the distillate from colophony resin. A few terpenes are derived from it. *p*-Cymene is much more important. It occurs in essential oils (oil of caraway, eucalyptus, etc.), and has been recognized as the fundamental substance of many important, naturally occurring terpenes and camphors (see Ch. 54).

HYDROCARBONS OF THE FORMULA $C_{11}H_{16}$. The most interesting compounds of this composition are pentamethylbenzene and *m*-*tert*-butyltoluene. The latter is the substance from which "toluene musk" is prepared (see p. 421):

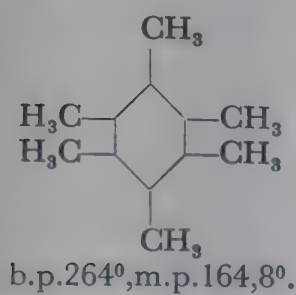


Pentamethylbenzene is converted by concentrated sulphuric acid into hexamethylbenzene and prehnitenesulphonic acid, with wandering of a CH_3 -group:



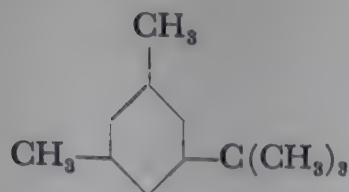
Besides pentamethylbenzene, durene and isodurene show the same wandering of a CH_3 -group under the influence of concentrated sulphuric acid. In both these cases, however, the wandering takes place within the molecule, and leads to the formation of prehnitene.

HYDROCARBONS OF THE FORMULA $C_{12}H_{18}$. Hexamethylbenzene is formed by the pyrogenic condensation of dimethylacetylene, or, together with lower homologues, from toluene and methyl chloride in the presence of aluminium chloride. It is also obtained quite smoothly by the action of hexabromo- or hexaiodobenzene on methylmagnesium salts:



In this compound there are no longer any hydrogen atoms directly linked to the carbon atoms of the nucleus. Hence it does not enter into the reactions which are characteristic of aromatic hydrocarbons. It is not sulphonated by sulphuric acid, or nitrated by nitric acid. By powerful oxidation, hexamethylbenzene gives benzenhexacarboxylic acid, *mellitic acid* (see Ch. 39).

1:3-Dimethyl-5-*tert*-butylbenzene (b.p. 200–202°), which may be obtained by the action of *isobutyl* bromide and aluminium chloride on *m*-xylene, is the parent substance of *xylene musk* (see p. 421):



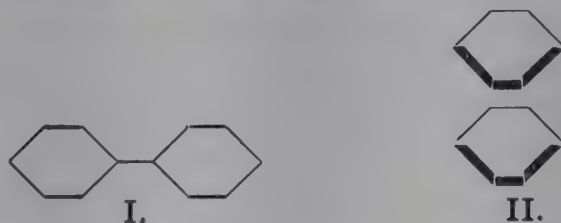
Hydrocarbons with more than one, uncondensed benzene nucleus

The simplest compound belonging to this class is biphenyl. This hydrocarbon is formed by passing benzene vapour through a red-hot tube (Berthelot) and is therefore also found in coal-tar. In order to favour the reaction, hot contact masses have recently been used. There are, in addition, many other ways of making biphenyl. One of them depends on the condensation of two molecules of iodobenzene or bromobenzene by means of sodium or copper:

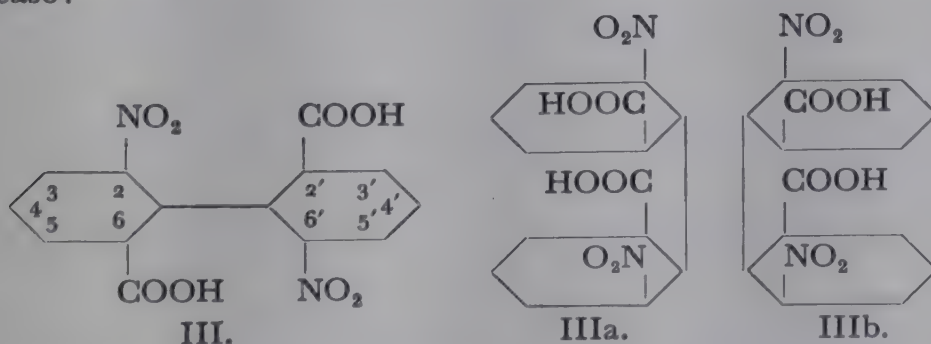


Biphenyl forms large, lustrous leaflets; m.p. 70° , b.p. 254° . Its chemical properties correspond to those of other aromatic hydrocarbons. It is readily nitrated and sulphonated. Numerous important dyes are derived from biphenyl.

The question of the spatial configuration of the diphenyl molecule has been raised by Kaufler. Starting from observations, which have now been shown by more recent work from many sides to be inaccurate, Kaufler came to the conclusion that the two benzene rings in biphenyl were not in one plane (formula I), but were arranged one above the other in space (formula II):

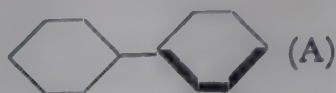


Kenner has been able to test the accuracy of this hypothesis. If it is correct, 2:6'-dinitrobiphenyl-2':6-dicarboxylic acid (III) must exist in enantiomorphous forms which are mirror images of each other (IIIa and IIIb). This is, in fact, the case:



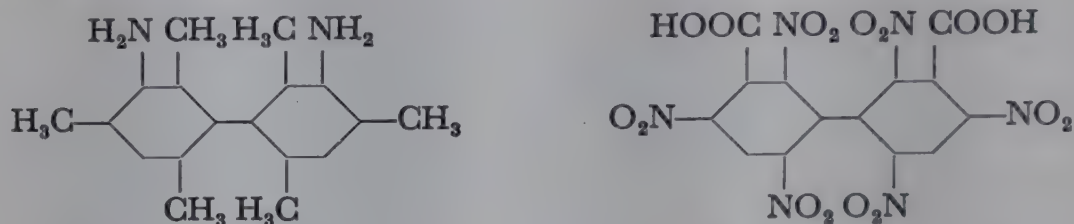
In spite of this the Kaufler formula for biphenyl is wrong. The asymmetry of certain biphenyl derivatives such as the 2:6'-dinitrobiphenyl-2':6-dicarboxylic acid mentioned above, depends rather on the fact that the planes of the two nuclei

of biphenyl are arranged transversely to each other in space, as is shown in the following diagram:



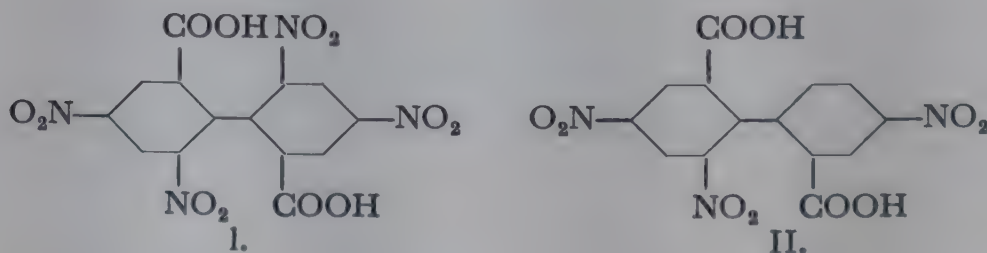
What causes the transverse positions of the benzene rings? According to earlier views it was the electrical charges of the substituents, attracting and repelling each other, which played the chief part. More probable, however, is the view of W. H. Mills that it is a matter of steric hindrance, i.e. that certain substituents, if they are in the 2:2', 6:6' positions in biphenyl, would not allow a coplanar arrangement of the benzene rings because there would not be room for the substituents. The benzene rings must therefore be at an angle to each other, and their rotation about the C-C axis is restricted. Of course, the electrical properties of the substituents may possibly exert some influence on the radii.

That the electrochemical character of the *ortho*-substituents, however, is not the chief cause of the perpendicular arrangement of the benzene rings has been proved by Roger Adams, who showed that compounds such as 2:2',4:4',6:6'-hexamethyl-3:3'-diaminobiphenyl and 2:2',4:4',6:6'-hexanitrobiphenyl-3:3'-dicarboxylic acid:



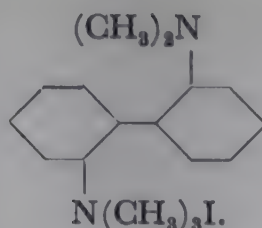
which contain *identical groups* in the 2:6- and 2':6'-positions, also occur in mirror-image isomerides.

The observation that the racemization of optically active biphenyl-derivatives, i.e. the mutual displacement of the two benzene rings from the perpendicular position, occurs more easily when not all four *ortho*-positions are occupied, but, say, only three of them, seems to confirm Mills' theory. Thus, *o,p,p'*-trinitro-diphenic acid (II) is more easily racemized than *o, p, o', p'*-tetranitro-diphenic acid (I):

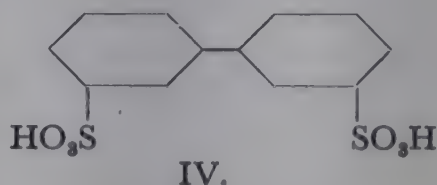
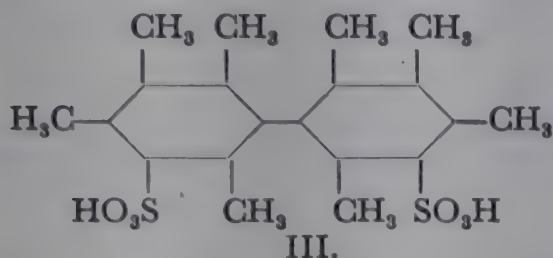


In the acid (II) there are only two groups which hinder the coplanar arrangement of the benzene rings.

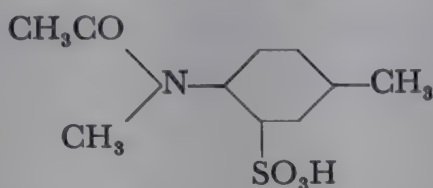
Finally, Turner has shown that under certain conditions, biphenyl compounds *di*-substituted in the 2:2'-position can also be resolved. If the radii of the substituents exceed a certain amount, rotation of the two benzene nuclei can no longer take place owing to steric hindrance, as a model will show. A coplanar structure thus becomes impossible. In fact, diphenyl benzidine-2:2'-disulphonate, which fulfils these conditions, has been resolved into enantiomorphous forms. This is true also of *o*-(2-dimethylamino-phenyl)-phenyl-trimethylammonium iodide:



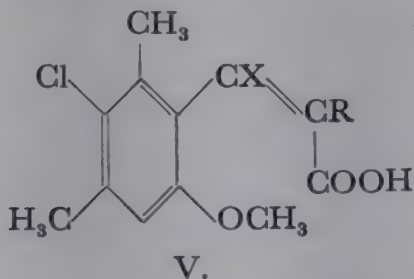
The cause of optical isomerism in the biphenyl series is especially well shown by the fact that III exists in optically active forms, whereas IV does not:



Mills has found that N-acetyl-N-methyl-*p*-toluidine-3-sulphonic acid exhibits an isomerism of a similar type to that referred to above.



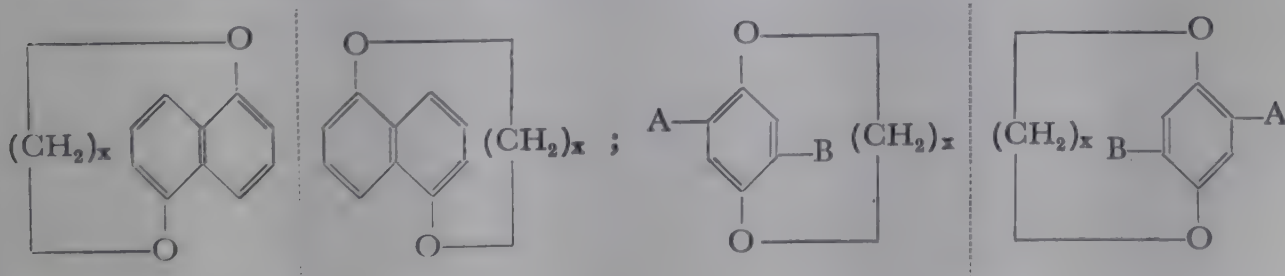
This compound can be resolved into optically active forms. The free rotation of the disubstituted amino-group is hindered by *ortho*-substitution, and this gives rise to molecular asymmetry. The above-mentioned sulphonic acid has a specific rotation of $\pm 6.0^\circ$, and the period for half-racemization is 5.25 hours. Also the resolvability of compounds of the type V into optically active forms depends on a similar cause, i.e. on the hindrance of the free rotation of the side chain by the substituents in the *ortho*-positions.



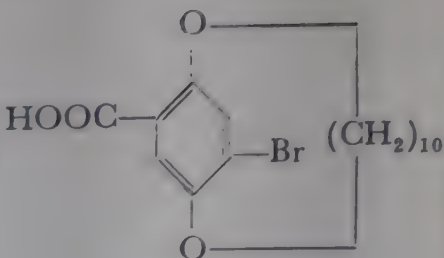
X = Cl, Br

R = H, CH₃

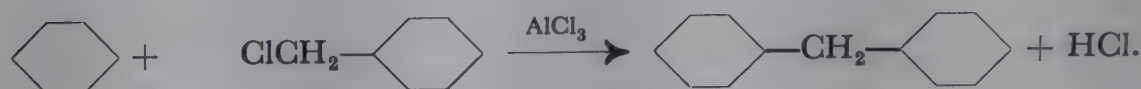
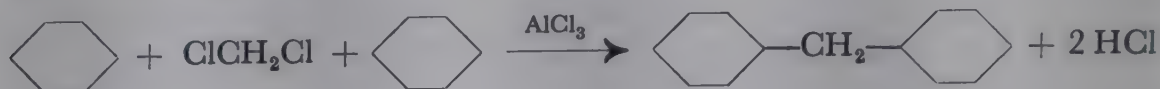
The inhibition of free rotation due to steric hindrance is also the cause of cases of stereoisomerism observed by Lüttringhaus with different aromatic compounds, in which medium-sized rings are attached to aromatic nuclei in such a way that free rotation of the aromatic nucleus around the connecting line of the extremities of the "bridge" is hindered by the bridge. In order to prevent the aromatic nucleus from "swinging through", the bridge has to be sufficiently short. In these cases, given a suitable structure or suitable substituents, asymmetry and, therefore, optical activity, will occur. The following types of compounds are examples of this kind:



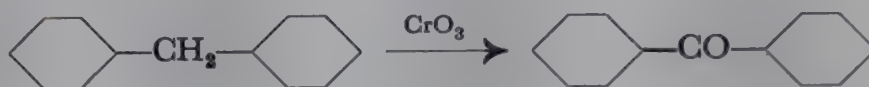
Among other compounds, the decamethylene ether of 4-bromogentisic acid has thus been obtained in optically active forms, which are very stable towards racemization; $[\alpha]_D^{17} = \pm 37.2^\circ$.



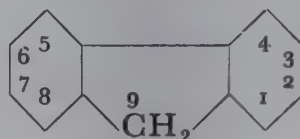
DIPHENYLMETHANE, $C_6H_5CH_2C_6H_5$. This compound is formed from benzene, methylene chloride, and aluminium chloride, or from benzene, benzyl chloride, and aluminium chloride:



The hydrocarbon crystallizes in needles, melting point, $26-27^\circ$, boiling point, 262° . It has a pleasant orange-like smell. Chromic acid oxidizes it to benzophenone (q.v.):

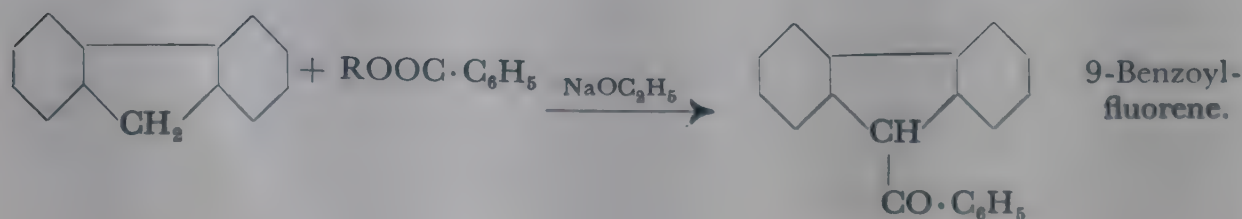
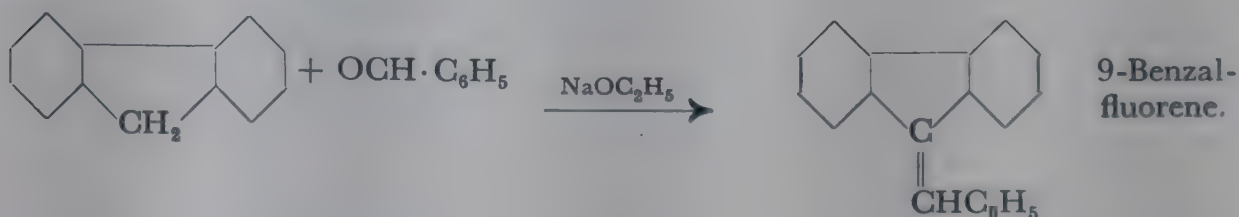


By passing diphenylmethane through a red-hot tube, hydrogen is eliminated and *fluorene* is formed:

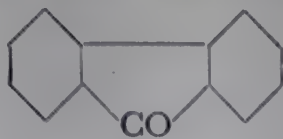


Similar pyrogenic condensations probably explain the presence of fluorene in coal-tar, from which it may be isolated in considerable quantities.

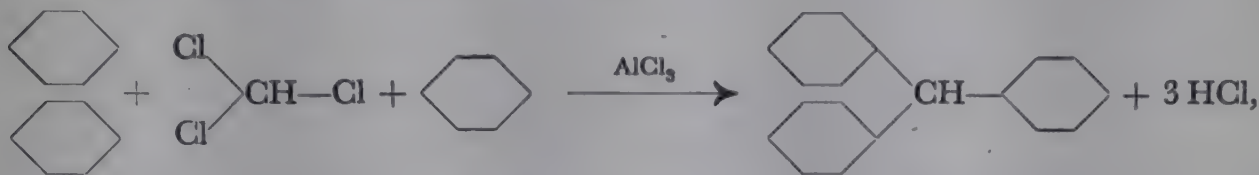
Fluorene is a stable hydrocarbon which melts at 115° , boils at 294° , and in alcoholic solution possesses a weak fluorescence. The methylene group between the benzene rings has reactive hydrogen atoms. It condenses with aldehydes and esters of the carboxylic acids in the presence of sodium ethylate. Thus, *9-benzalfluorene* is formed from fluorene and benzaldehyde, and *9-benzoylfluorene* from fluorene and esters of benzoic acid:



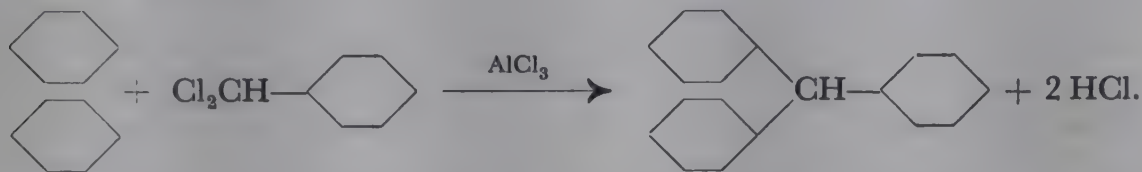
On oxidation, fluorene gives the yellow fluorenone:



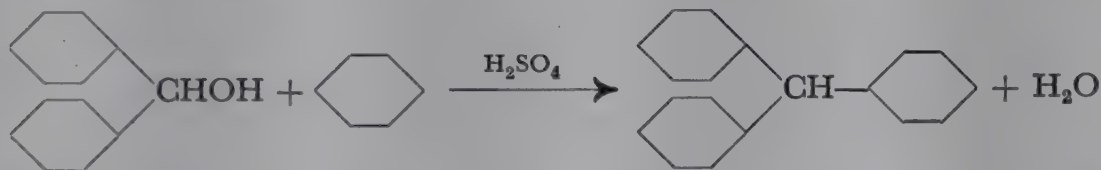
TRIPHENYLMETHANE, $(C_6H_5)_3CH$. Various syntheses are available for this hydrocarbon, the parent substance of the important group of triphenylmethane dyes. One depends on the condensation of three molecules of benzene with chloroform in the presence of aluminium chloride:



another is the application of the Friedel-Crafts reaction to a mixture of benzene and benzal chloride:

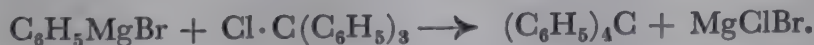


Triphenylmethane can also be obtained by the action of three molecules of phenylmagnesium bromide on chloroform, or the condensation of diphenylcarbinol and benzene with elimination of water, brought about by means of concentrated sulphuric acid:



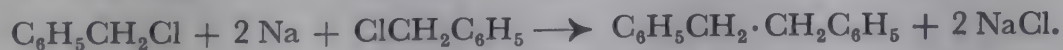
The compound crystallizes from benzene with benzene of crystallization. From alcohol two physically isomeric forms can be obtained, one stable and the other labile, which crystallize differently. Triphenylmethane is very readily oxidized by chromic acid. Triphenylcarbinol, $(C_6H_5)_3C \cdot OH$, is thus formed (see Ch. 48).

TETRAPHENYLMETHANE, $(C_6H_5)_4C$. To prepare the fully phenylated methane a solution of phenylmagnesium bromide is made to react with triphenyl-chloromethane (Gomberg):



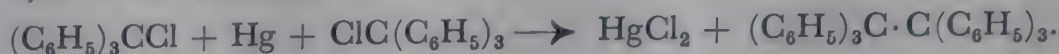
The hydrocarbon forms colourless crystals, m.p. 285° , and is very stable.

DIPHENYLETHANE, BIBENZYL, $C_6H_5CH_2CH_2C_6H_5$, m.p. 52° , is readily obtained by Fittig's reaction from benzyl chloride and sodium:

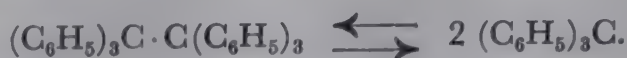


Like *tetraphenylethane*, $(C_6H_5)_2CH \cdot CH(C_6H_5)_2$, it shows no tendency to dissociate. On the other hand, *pentaphenylethane*, $(C_6H_5)_3C \cdot CH(C_6H_5)_2$, and *hexaphenylethane*, $(C_6H_5)_3C \cdot C(C_6H_5)_3$, are of interest from the point of view of valency because of their decomposition into "free radicals".

Aromatic hydrocarbons with "trivalent" carbon. By shaking *triphenylmethyl chloride*, $(\text{C}_6\text{H}_5)_3\text{CCl}$, in an indifferent solvent (benzene) and in absence of air, with metals, such as mercury, molecular silver or zinc, a yellow solution is formed, from which, on concentration, colourless crystals separate. These are hexaphenylethane, $(\text{C}_6\text{H}_5)_3\text{C} \cdot \text{C}(\text{C}_6\text{H}_5)_3$:



Hexaphenylethane, however, partially dissociates in solution within a few seconds, as Gomberg showed, into yellow *triphenylmethyl*, $(\text{C}_6\text{H}_5)_3\text{C}$, which, in terms of the classical theory of valency contains trivalent carbon, and is to be regarded as a "radical":

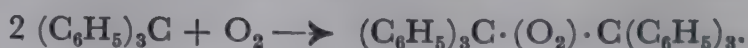


On the basis of the modern electronic theory, a *radical* may be defined as a group of atoms in which one atom (C-atom, N-atom) does not possess a complete octet of electrons, being usually one *electron* short. An infallible characteristic of the radical nature of a compound is its paramagnetism.

By loading the two ethane carbon atoms with six heavy phenyl radicals in hexaphenylethane, the affinity available for linking the two carbon atoms has obviously become so small that even the introduction of a solvent is sufficient, partially to break down the linkage.

The equilibrium between hexaphenylethane and triphenylmethyl is dependent on the solvent and the temperature. Warming favours the dissociation, and when cooled the reverse reaction takes place. In ether at room temperature the ratio of colourless hexaphenylethane to yellow triphenylmethyl is about 10 : 1.

In addition to its yellow colour, its paramagnetism, and the association mentioned above, the behaviour of its solutions towards other substances confirms the unsaturated nature of triphenylmethyl, and the view that it is a radical. On shaking a yellow solution of triphenylmethyl with oxygen or air, the colour rapidly disappears, colourless triphenylmethyl peroxide being formed:



On exclusion of air, however, the yellow colour soon returns, because some of the hexaphenylethane, still present, again dissociates into triphenylmethyl.

Triphenylmethyl readily takes up iodine (with formation of triphenyl-iodomethane), and nitrogen dioxide. Also ethers, esters, benzene, and even "saturated" hydrocarbons, e.g. *cyclohexane*, can combine with triphenylmethyl forming molecular compounds (Gomberg). Physical properties also point to a dissociation of hexaphenylethane in solution to triphenylmethyl; for example, the compound does not obey Beer's law, according to which the intensity of colour of a solution does not vary on dilution provided that the height of the column of liquid viewed is correspondingly increased. Hexaphenylethane solution shows, on the contrary, a deepening of colour on dilution, which is due to the increased dissociation of colourless hexaphenylethane into yellow triphenylmethyl on dilution.

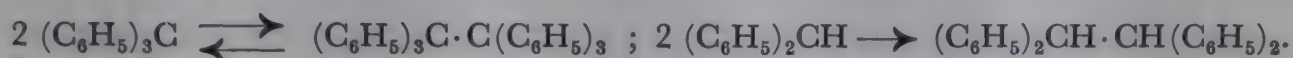
The surprising ease of dissociation of hexaphenylethane into triphenylmethyl gave rise to a large number of experiments, in which it was sought to discover how the tendency of the ethane carbon linkage to dissociate varied if other aromatic radicals were introduced in place of the six phenyl groups of hexaphenylethane (Schlenk). It was found that, in general, the dissociation increased with increasing

size of the substituting groups. Thus, *tri-p-biphenyl-methyl* $\left(\text{C}_6\text{H}_4\text{--C}_6\text{H}_4\right)_3\text{C}$, exists in solution to a considerable extent (about 26%) as the monomolecular, coloured form. The solutions appear violet by transmitted light, but greenish in thin layers.

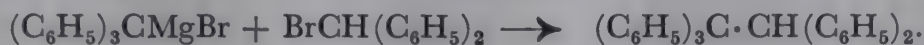
Whilst *tri-p-biphenyl-methyl* thus appears to be much more stable than triphenylmethyl, in the case of *pentaphenylethane*, $(\text{C}_6\text{H}_5)_3\text{C--CH}(\text{C}_6\text{H}_5)_2$, the readiness to dissociate is much reduced. The dissociation is first noticeable in high-boiling solvents (anisole, ethyl benzoate) and even then is not considerable:



Of the two radicals thus produced, the first polymerizes partially to hexaphenylethane, and the latter *completely* to tetraphenylethane:

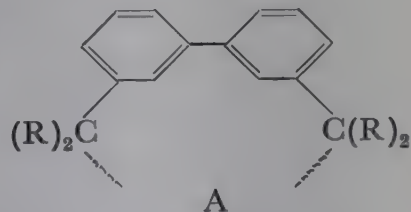


Pentaphenylethane is best prepared by the method of W. E. Bachmann from triphenylmethylmagnesium bromide and diphenylbromomethane:



It has also been possible (Ziegler) to prepare a number of diaryl-alkyl-methyls in which, in place of phenyl groups, residues occupying a smaller space, but of greater unsaturation are present in the molecule. Thus, 1:1:3:3-tetraphenylallyl, $(\text{C}_6\text{H}_5)_2\text{C--CH=}$
 $\text{C}(\text{C}_6\text{H}_5)_2$, has been obtained, in which the equilibrium is strongly displaced in favour of the radical. Also when two phenyl groups of hexaphenylethane are replaced by aliphatic or alicyclic groups, as, for example, in tetraphenyl-dimethyl-ethane, $(\text{C}_6\text{H}_5)_2(\text{CH}_3)\text{C}\cdot\text{C}(\text{CH}_3)(\text{C}_6\text{H}_5)_2$, or tetraphenyl-dicyclohexyl-ethane, $(\text{C}_6\text{H}_5)_2(\text{C}_6\text{H}_{11})\text{C}\cdot\text{C}(\text{C}_6\text{H}_{11})(\text{C}_6\text{H}_5)_2$, the molecule may partially dissociate into radicals.

Further, some so-called *biradicals* of the triphenylmethyl series have been produced, such as those of the type A, which contain two C-atoms with incomplete electron octets.

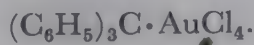


That the fourth valency in the triarylmethyls, $(\text{Aryl})_3\text{C}$, is particularly weak is moreover confirmed by the properties of the triarylmethyl halides, $(\text{Aryl})_3\text{C}\cdot\text{X}$ (X = halogen).

In these compounds the halogen atom is not firmly linked to the carbon as in other organic halides, but has an ionic character as in inorganic salts. In liquid sulphur dioxide, triphenylmethyl chloride, $(\text{C}_6\text{H}_5)_3\text{CCl}$, is dissociated into triphenylmethyl ions, $(\text{C}_6\text{H}_5)_3\text{C}^+$, and chlorine ions, Cl^- . Like inorganic chlorides, triphenylmethyl halides show "double decomposition" with acids and salts:



and form molecular compounds with gold and platinum chlorides, e.g.

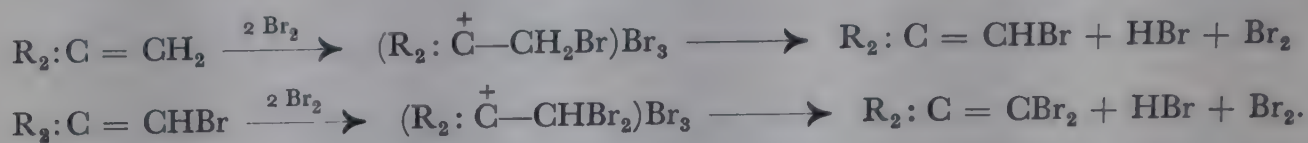


The triphenylmethyl halides have therefore been called "carbonium" salts, expressing the fact that there is a kind of salt formation at the carbon atom (see also the constitution of the triphenylmethane dyes, Ch. 48).

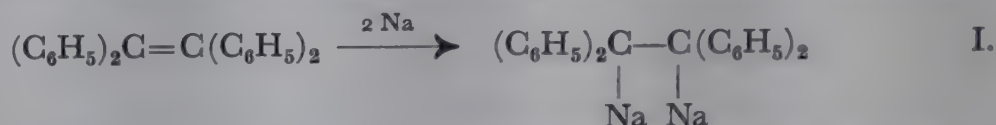
Unsaturated aromatic hydrocarbons

The unsaturated aromatic hydrocarbons contain, in general, very reactive double bonds and are therefore capable of many different kinds of reactions.

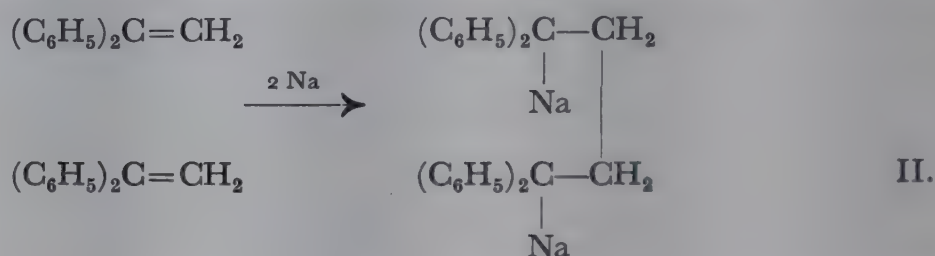
Thus, by the action of bromine, the diarylethylenes of the general formula $R_2C = CH_2$, are progressively substituted, coloured, salt-like intermediate compounds being formed:




The unsaturated aromatic hydrocarbons also react with lithium, sodium, and potassium in the absence of air, often very readily. In general those carbon atoms which are linked with aryl groups (sometimes also with unsaturated aliphatic groups) are capable of linking with the alkali metal. The reaction can proceed in such a way that two sodium atoms are taken up for each ethylenic linkage:



or in such a way that only one sodium atom is added for each double bond, a doubling of the molecule taking place simultaneously. (Schlenk, Conant and Blatt):



In such organic alkali-metal compounds, the alkali-metal atoms can be replaced by hydrogen (by the action of water), and by the carboxyl group (by the action of carbon dioxide). Methyl iodide reacts with (I) with re-formation of the original unsaturated hydrocarbon. If, however, the sodium atoms are not adjacent, as in (II), CH_3 enters in their place.

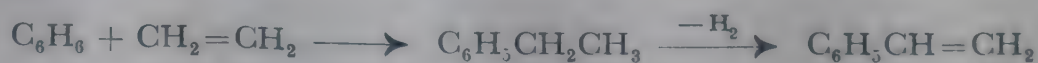
STYRENE,  $-CH = CH_2$. This unsaturated hydrocarbon (boiling point 146°) is found in storax (a kind of balsam). It is formed by slow distillation of cinnamic acid:



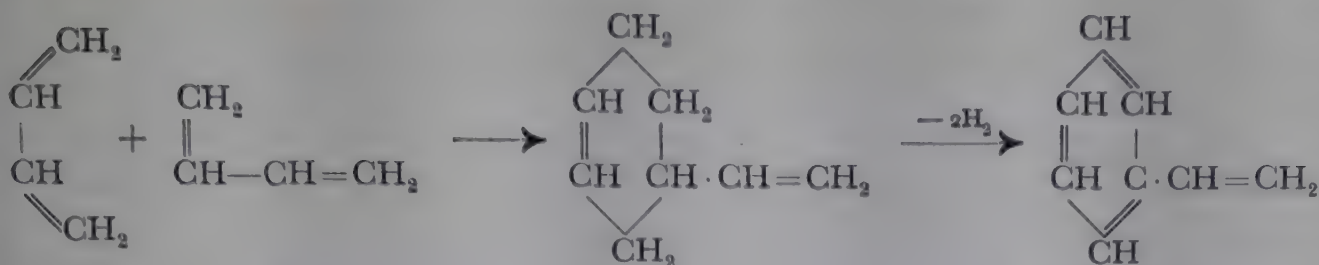
or from benzaldehyde by the following method:



Industrially, styrene is nowadays chiefly produced by catalytic dehydrogenation of ethylbenzene, which, in turn, is obtained by catalytic addition of ethylene to benzene:



Styrene may also be obtained technically by polymerization of butadiene:




Styrene is strongly unsaturated, a fact which is shown by the ease with which it forms different polymers. On long heating, or by the action of light it forms the highly polymerized "*metastyrene*", or "*polystyrene*", a mixture of products of different degrees of polymerization. Treatment with acids (warm hydrochloric acid, or a mixture of acetic and sulphuric acids) converts styrene into liquid *distyrene*, of which the constitution is expressed by the formula $\text{C}_6\text{H}_5\text{CH}=\text{CHCH}(\text{CH}_3)\text{C}_6\text{H}_5$. Heating with sulphuric acid displaces the double bond, and the isomeric hydrocarbon $\text{C}_6\text{H}_5\text{CH}_2\text{CH}=\text{C}(\text{CH}_3)\text{C}_6\text{H}_5$ is formed. A "*solid distyrene*",



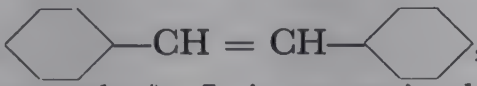
is also known (Stobbe) as well as other polymers of styrene.

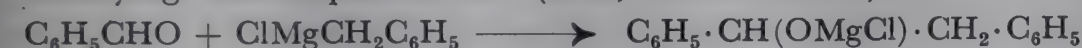
Important plastics are now manufactured from the polystyrenes, and are used as electrical insulators, for the manufacture of buttons, etc.

PHENYLACETYLENE,  $\text{C}\equiv\text{CH}$, is formed by the distillation of phenylpropionic acid (see Ch. 38):

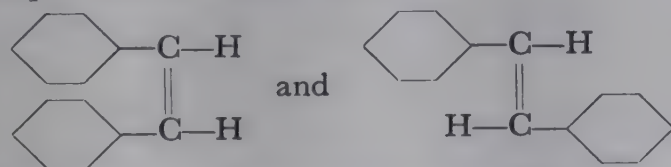


As it is a monosubstituted acetylenic compound, phenylacetylene forms a silver and a copper salt.

STILBENE, , α,β -diphenylethylene, is obtainable by various methods. It is conveniently prepared by the action of benzylmagnesium chloride on benzaldehyde, and distillation of the product after acidifying with sulphuric acid (Hell, Meisenheimer):

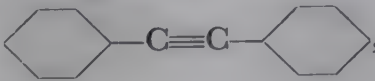


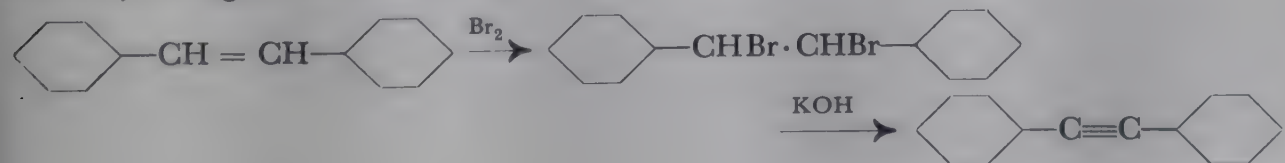
Stilbene melts at 124° and boils at 306° – 307° . Being a derivative of ethylene, it has a geometrical isomeride, *isostilbene* (an oil, boiling point 142° – 143° (21 mm)). The two compounds have the formulæ:



of which the first (*cis* form) represents *isostilbene*, and the second (*trans*) stilbene.

Stilbene is the more stable form. It is converted by the action of ultra-violet light into the energy-rich, and therefore less stable, *isostilbene*.

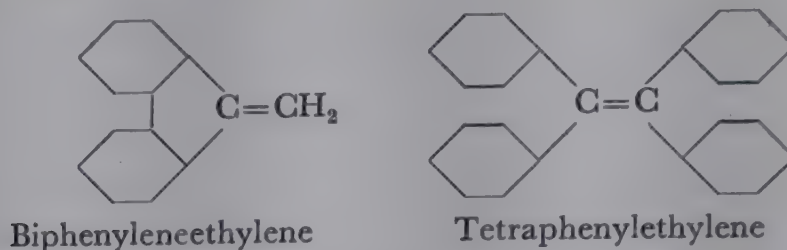
TOLAN, , "*diphenylacetylene*" can be obtained from stilbene, through dibromostilbene:



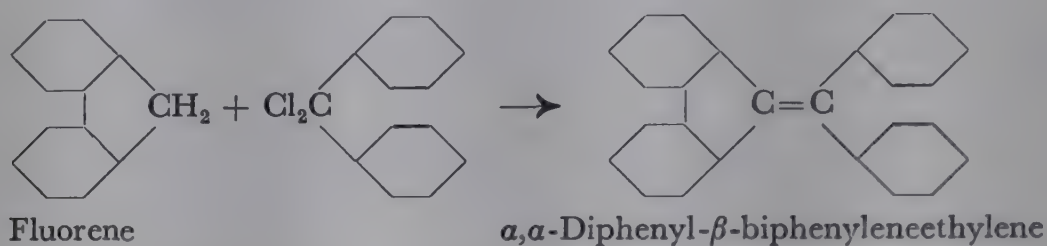
As it is a *disubstituted* acetylenic derivative it does not form metal salts. It melts at 60° .

Since the above-mentioned unsaturated aromatic hydrocarbons absorb particularly in the invisible part of the spectrum, they appear colourless, but suitable replacement of the hydrogen atoms of ethylene by phenyl, and especially biphenyl radicals gives rise to *coloured hydrocarbons*.

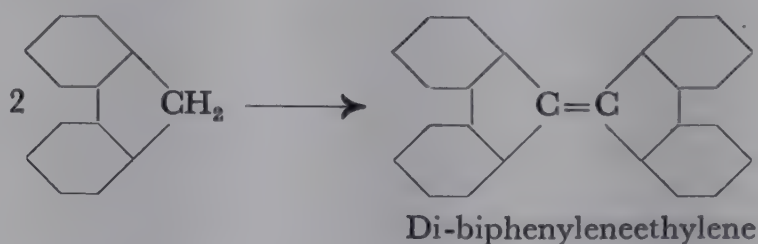
Biphenyleneethylene is still colourless, as is also *tetraphenyleneethylene*, which forms very refractive crystals:



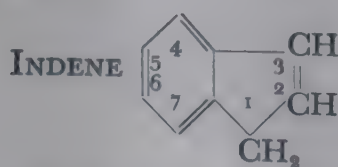
On the other hand, *α,α -diphenyl- β -biphenyleneethylene*, which can be prepared from fluorene and diphenyldichloromethane, is intense yellow in solution. The crystals are almost colourless:



Di-biphenyleneethylene has a still deeper red colour. It is obtained from fluorene by heating with lead oxide:

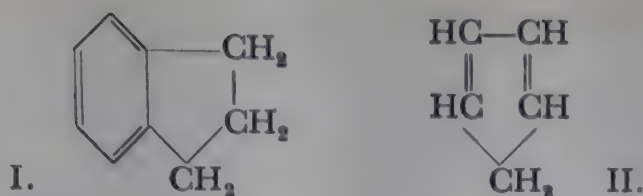


It follows that the linking of two phenyl groups together in this group of hydrocarbons causes a deepening of colour. All these hydrocarbons contain the same chromophoric system, $\begin{array}{c} =\text{C} \\ \diagdown \\ \text{C}=\text{C} \\ \diagup \\ =\text{C} \end{array}$, like the fulvenes, dealt with elsewhere, see Ch. 53.



This compound occurs in coal-tar, and can be readily separated from it, as it forms a difficultly soluble, well-crystallized picrate. It has also been detected in some essential oils, and in mineral oil.

Indene crystallizes on cooling. It melts at -2° , and boils at 182° . It is a rather unstable hydrocarbon, and it rapidly polymerizes even at ordinary temperatures and in the dark. In the air indene takes up oxygen. The existence of a sodium compound, indenylsodium, $\text{C}_9\text{H}_7\text{Na}$, is remarkable. It gives, on alkylation with methyl iodide, 1-methylindene. Hydrogen in the presence of nickel reduces the hydrocarbon to hydrindene (I):

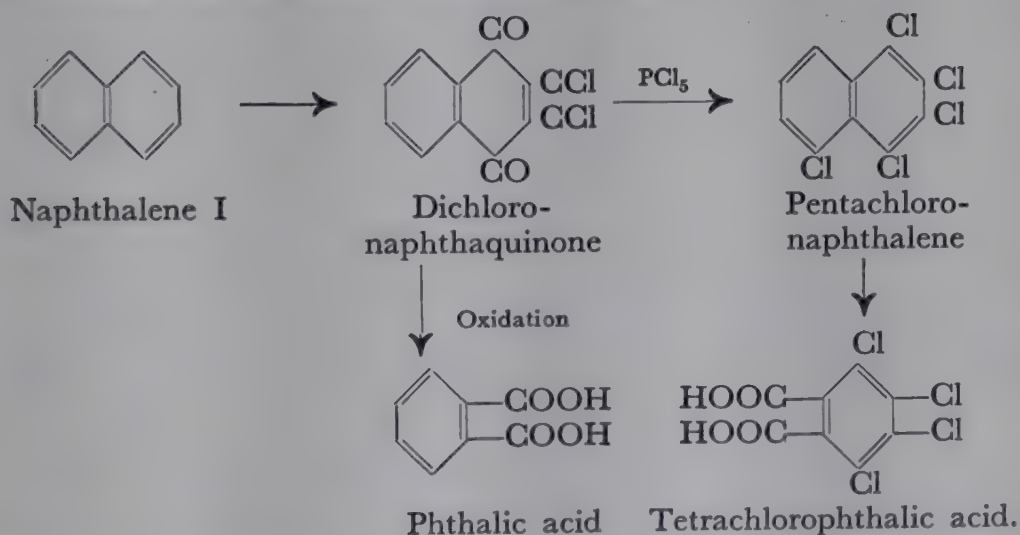


Indene contains the *cyclopentadiene* (see Ch. 53) ring system II. The methylene group of *cyclopentadiene* lying between two carbon atoms linked by double bonds is very reactive. The same is true of the methylene group in indene. It condenses, for example, with benzaldehyde in the presence of sodium ethylate to give 1-benzal-indene.

Aromatic hydrocarbons with condensed benzene nuclei¹

Naphthalene,² $C_{10}H_8$. Naphthalene is contained in large quantities in coal-tar, and is obtained from it by the method already described.

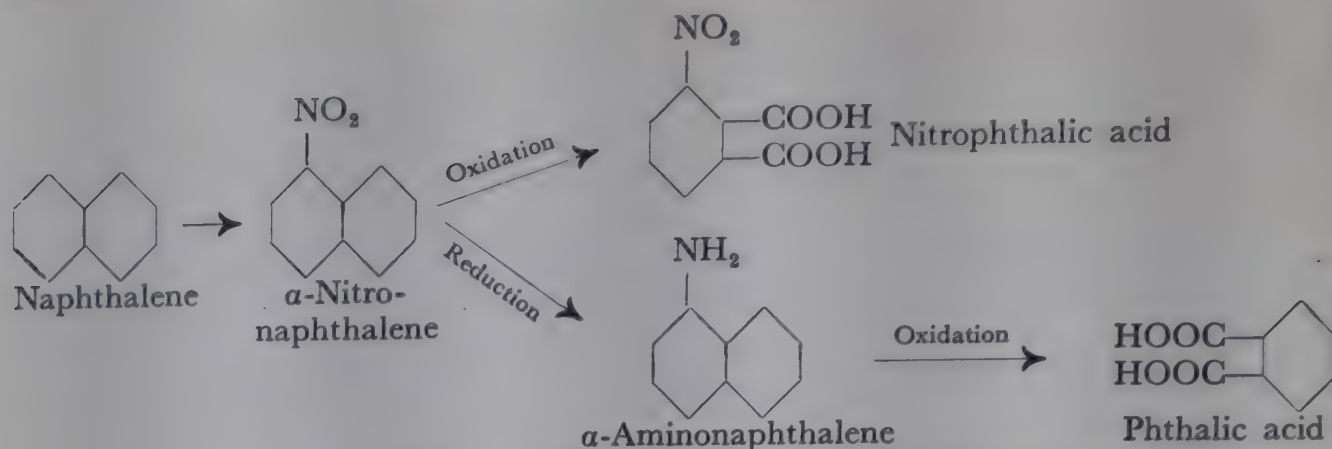
Erlenmeyer sen. was the first to give a correct picture of the constitution of this hydrocarbon. It was proved by Graebe. By oxidation of *dichloronaphthaquinone*, obtained from naphthalene, Graebe obtained *phthalic acid*. The existence of a benzene ring in naphthalene was thus proved. If dichloronaphthaquinone is treated with phosphorus pentachloride, a pentachloronaphthalene is formed, which, on oxidation, gives *tetrachlorophthalic acid*. By this second degradation it was shown that dichloronaphthaquinone contains a second chlorinated benzene nucleus, and that therefore the naphthalene molecule consists of two ring systems, each of which can be isolated as a benzene ring by destroying the other. The only possible formula for naphthalene is therefore (I).



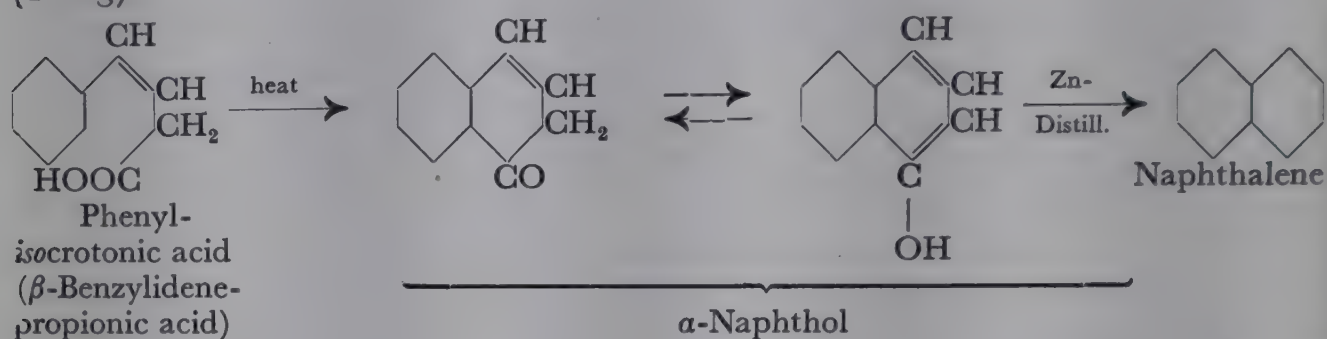
The following proof of the structure of naphthalene is based on similar lines. By nitration of naphthalene, nitronaphthalene is formed, and this on oxidation gives *nitrophthalic acid*. Therefore nitronaphthalene contains a nitrogen-containing benzene nucleus. If nitronaphthalene is reduced to aminonaphthalene, and the latter is submitted to oxidation, *phthalic acid* can be isolated. There must, therefore, also be a nitrogen-free benzene ring in nitronaphthalene. Nitronaphthalene and naphthalene must therefore be built up of two benzene rings.

¹ E. CLAR, *Aromatische Kohlenwasserstoffe. Polycyclische Systeme*, Berlin, (1941).

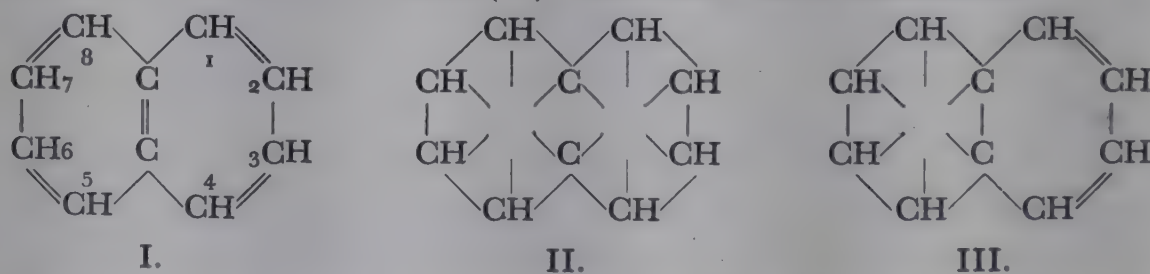
² VAN DER KAM (new ed. by F. Reverdin and H. Fuda), *Tabellarische Übersicht über Naphtalinderivate*, The Hague, (1927).



A synthesis of naphthalene of which the course is straightforward, and which proceeds smoothly, confirms the formula of the compound derived by degradation. Phenylisocrotonic acid gives, on heating, α -naphthol (α -hydroxynaphthalene) with elimination of water, and this, on distillation with zinc dust gives naphthalene (Fittig):

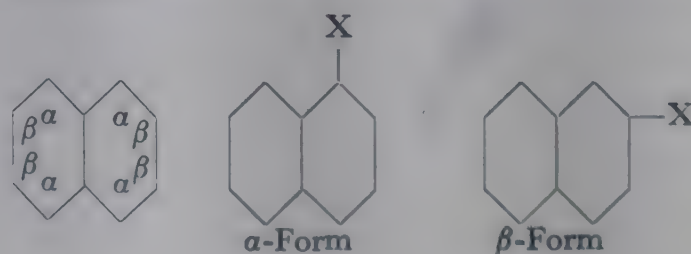


The naphthalene molecule consists, therefore, of two benzene nuclei condensed in the *ortho*-positions. What views are adopted with regard to the binding relationships within the molecule will be intimately connected with the conception of the valency distribution within the benzene ring. In addition to the most common formula for naphthalene (I), based on Kekulé's formula for benzene, formerly also a "centric" formula (II), and others were considered:

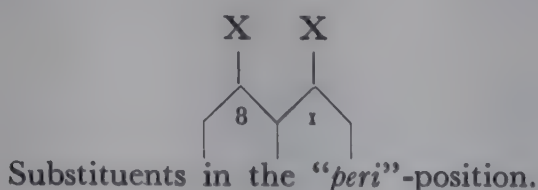


The electronic formula of naphthalene follows closely that of benzene (q.v.), i.e. all the C-atoms of naphthalene are alternately bound by one and two electron pairs, and the different mesomeric forms are in a state of resonance.

It follows from the structural formula of naphthalene that the eight hydrogen atoms of this hydrocarbon are not equivalent, but fall into two groups, the α - and the β -hydrogen atoms. *Monosubstitution* products of naphthalene therefore always exist in two isomeric forms:



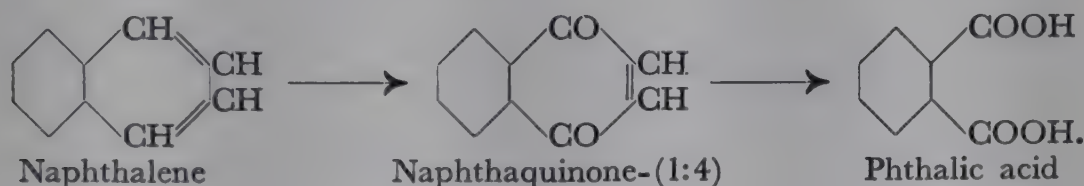
For *disubstituted* naphthalene derivatives theory requires the existence of ten isomerides when the substituents are identical. If the two substituents are different there are fourteen possibilities (see table VI). The 1:8 position in naphthalene shows in many respects similarity to the *ortho*-position in the benzene ring. It is called the *peri*-position.



Naphthalene crystallizes in large, colourless tablets. It has a strong, characteristic smell. It melts at 81° , and boils at 217° . It is almost insoluble in water, but is readily soluble in organic solvents.

Its chemical character is definitely "aromatic". It can be nitrated and sulphonated, different mono-, di-, or polysubstitution products being formed according to the conditions. (See nitronaphthalenes, naphthalenesulphonic acids, etc.). Chlorine successively replaces all the hydrogen atoms of naphthalene. The first reaction product is α -chloronaphthalene, and the highest chlorinated compound is perchloronaphthalene, $C_{10}Cl_8$.

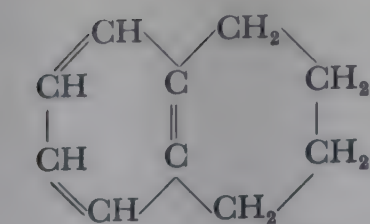
On oxidation naphthalene yields either naphthaquinone-(1:4), or phthalic acid, according to the oxidizing agent and the conditions under which it is used:



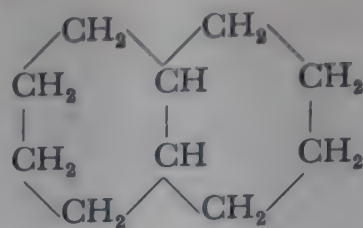
The breakdown of naphthalene to phthalic acid which is brought about, for example, by heating the naphthalene with fuming sulphuric acid and a little mercury, or by heating the hydrocarbon with atmospheric oxygen in the presence of a metal oxide acting as a catalyst, proceeds quite smoothly, and is very important technically, since phthalic acid (q.v.), an important substance in the synthesis of dyes, is readily available by this method.

The reduction of naphthalene has also become a process of industrial importance within recent years. The reaction can be carried out with hydrogen and finely divided nickel at high temperatures in autoclaves (G. Schroeter). A condition for the success of the reaction is a very pure naphthalene. To remove catalyst poisons from the naphthalene it is fused with sodium and subsequently distilled.

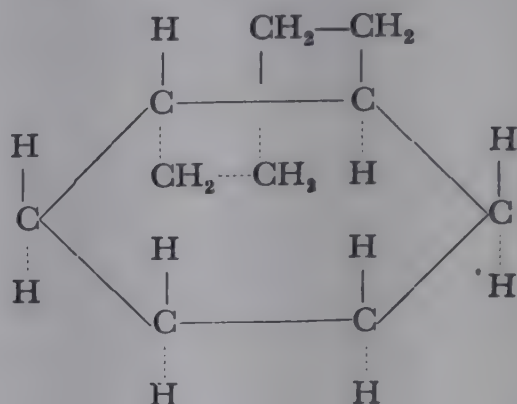
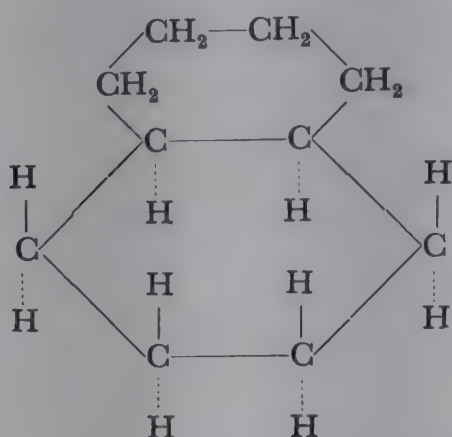
The reduction products vary according to the conditions of the hydrogenation, *dihydronaphthalene*, *tetrahydronaphthalene*, or *decahydronaphthalene* (Leroux, Sabatier and Senderens, G. Schroeter) being obtained. The last two are prepared commercially, and are used under the names "*tetralin*" and "*decalin*", as additions to motor fuels, etc. and as solvents, extracting agents and diluting media (used, for example, in the lacquer and shoe-cream manufacturing industries):



Tetralin, b.p. 205–207°

Decalin, b.p. *cis*-form 194.6°,
trans-form 185.5°

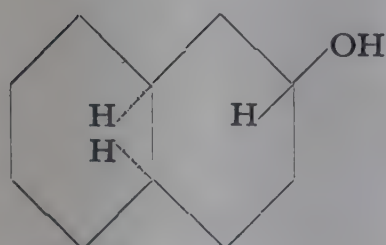
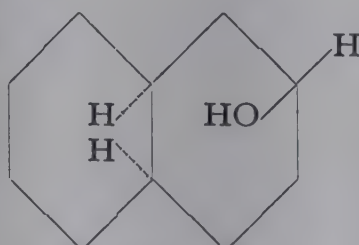
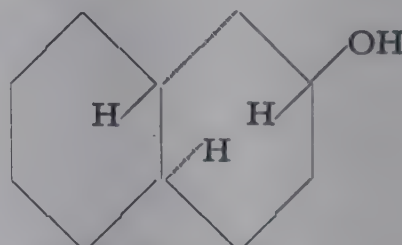
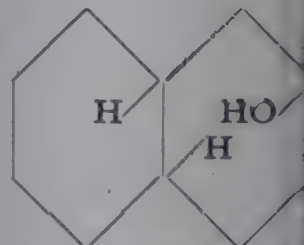
DECAHYDRONAPHTHALENE and its derivatives have recently gained attention on account of their interesting steric relationships. Mohr had already pointed out that the existence of more than one strain-free decahydronaphthalene appeared to be possible if the two ring were not coplanar, but were arranged, for example, as follows:



Hückel then succeeded in obtaining by reduction of β -naphthol,

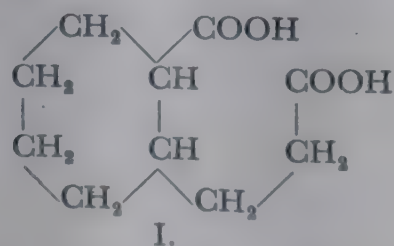


(see p. 442) four racemic decahydro- β -naphthols (decalols), the isomerism of which can be expressed by the following formulæ:

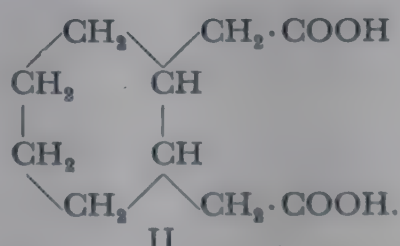
*cis*-decalol, m.p. 105°*cis*-decalol, m.p. 17°*trans*-decalol, m.p. 75°*trans*-decalol, m.

The *cis*-decalols gave, on oxidation, two acids of melting point 101° and 159°–161°, respectively. Two acids, of melting points 143° and 167° respectively were isolated by the decomposition of the *trans*-decalols.

The acids of melting point 101° and 143° proved to be the *cis*- and *trans*-hexahydrohydrocinnamic-*ortho*-carboxylic acids (I); the other two acids were the *cis*- and *trans*-hexahydrophenylene-diacetic acids (II):



I.

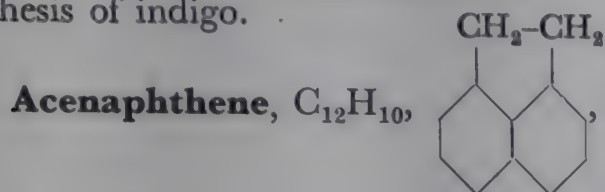


II.

The fact that *cis-trans* isomeric acids are formed by oxidative degradation of the decahydro- β -naphthols, proves the *cis-trans* isomerism of these hydrogenated naphthols.

Their two carbon rings do not, therefore, lie in one plane. Similar pairs of isomerides are found for many other compounds, and for decalin itself. They often rearrange one into the other. Thus *cis*-decalin is quantitatively converted into the *trans*-form by aluminium chloride.

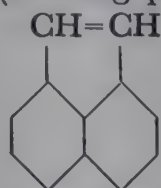
Naphthalene itself is the starting point for the preparation of many dyes, and intermediates in dye manufacture. Phthalic acid prepared from it is used in the synthesis of indigo.



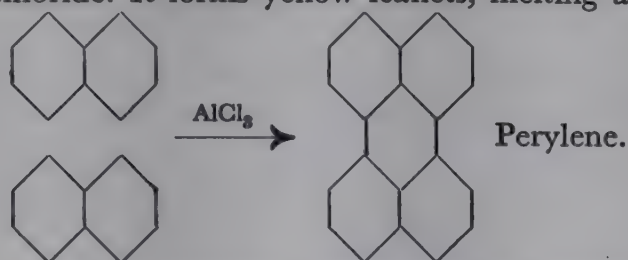
was discovered by Berthelot in coal-tar, where it collects in the heavy oil, and particularly in the anthracene

oil fractions. It is formed synthetically if α -ethyl-naphthalene or a mixture of naphthalene and ethylene, is passed through a red-hot tube. It melts at 95° and boils at 278° . Acenaphthene is used technically for the preparation of acenaphthenequinone by oxidation, the latter being used in the manufacture of vat dyes.

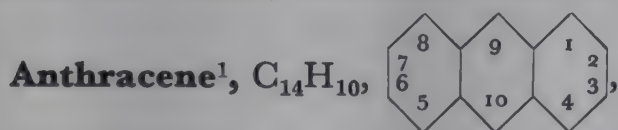
If acenaphthene is distilled over red-hot lead oxide, dehydrogenation takes place and *acenaphthylene* is formed (melting point 92°).



Perylene. This hydrocarbon is formed by the condensation of naphthalene by means of aluminium chloride. It forms yellow leaflets, melting at 264° :



Attempts have recently been made to use perylene in the synthesis of dyes.

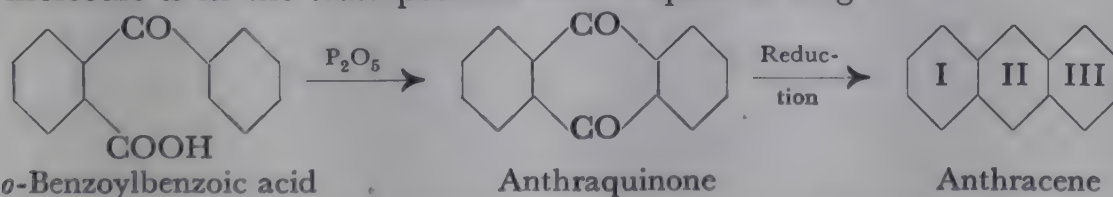


forms one of the chief constituents of the anthracene oil of coal-tar, from

which it is obtained technically. Large groups of dyes are derived from it.

The anthracene molecule consists of three benzene rings fused in the *ortho*-positions. The proof of this is furnished by the following syntheses:

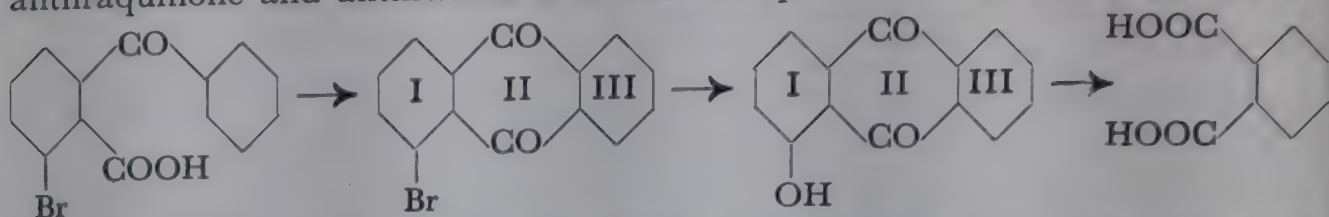
o-Benzoylbenzoic acid, obtained from phthalic acid, gives anthraquinone when fused with phosphorus pentoxide, and the anthraquinone gives anthracene on reduction. Since the two carboxyl groups of phthalic acid are in the *ortho*-position with respect to each other, the synthesis shows that ring II of the anthracene molecule is in the *ortho*-position with respect to ring I:



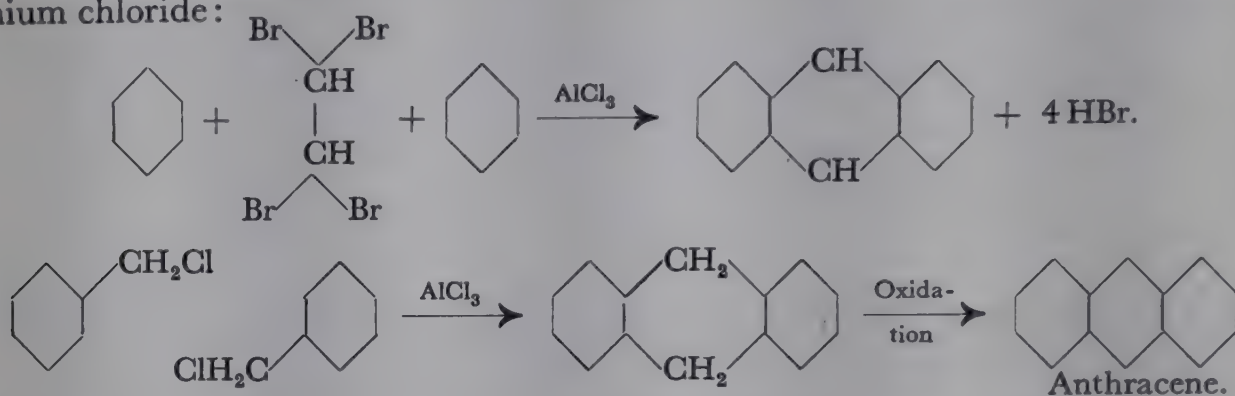
If, instead of *o*-benzoylbenzoic acid, an *o*-benzoyl-bromobenzoic acid is chosen

¹ See E. DE BARRY-BARNETT, *Anthracene and Anthraquinone*, London, (1921).

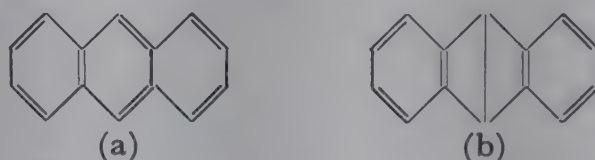
for the ring closure, a bromoanthraquinone is formed. On fusion with alkali this is converted into a hydroxyanthraquinone, which can be broken down by oxidation into phthalic acid. This phthalic acid can only have arisen from the bromine-free ring III of the bromoanthraquinone, and since in phthalic acid the two carboxyl groups are in the *ortho*-position, it follows that ring III of anthraquinone and anthracene is in the *ortho*-position with regard to ring II.



In addition to the above synthesis of anthracene through anthraquinone there are still other direct, synthetic methods of making anthracene. It can be obtained, for example, by the Friedel-Crafts reaction from benzene, tetrabromoethane, and aluminium chloride (Anschütz), or from benzyl chloride and aluminium chloride:



The valency relationships in the polycyclic anthracene molecule are as uncertain as those in benzene and naphthalene. Anthracene is usually given Hinsberg's formula (a). Formula (b) in which the middle carbon atoms (9 and 10) of the anthracene are joined by a bridge, is out of the question owing to the great strain which would exist in such a structure:



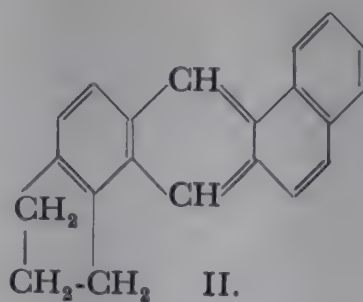
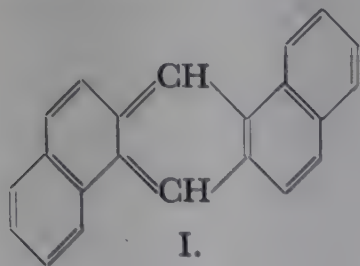
The positions 1, 4, 5, and 8 are the α -positions of the anthracene molecule; 2, 3, 6, and 7 are the β -positions, and 9 and 10 are called the *meso* (*ms*)-positions. There are, therefore, three structural isomerides of monosubstitution products of anthracene (see table VI).

Anthracene forms colourless plates, which melt at 216° , and possess a violet fluorescence. Anthracene solutions (e.g. in alcohol) also show a weak fluorescence. Oxidizing agents (chromic acid, manganic salts, etc.) readily attack the substance and convert it into anthraquinone (see Ch. 47). The hydrocarbon is also easily reduced. Sodium amalgam reduces it to 9:10-dihydroanthracene, and by means of hydrogen and a catalyst it can be progressively reduced to the tetrahydro-, octahydro-, decahydro-, and perhydro- ($C_{14}H_{24}$) compounds.

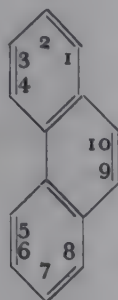
Many natural products are derivatives of anthracene, e.g. alizarin, the cochineal dye, chrysophanic acid, etc.

Some of the synthetic anthracene derivatives, such as 1:2:5:6-dibenzan-

thracene (I) and 5:6-*cyclopenteno*-1:2-benzanthracene (II) give rise to cancerous growths (Cook, Dodds):



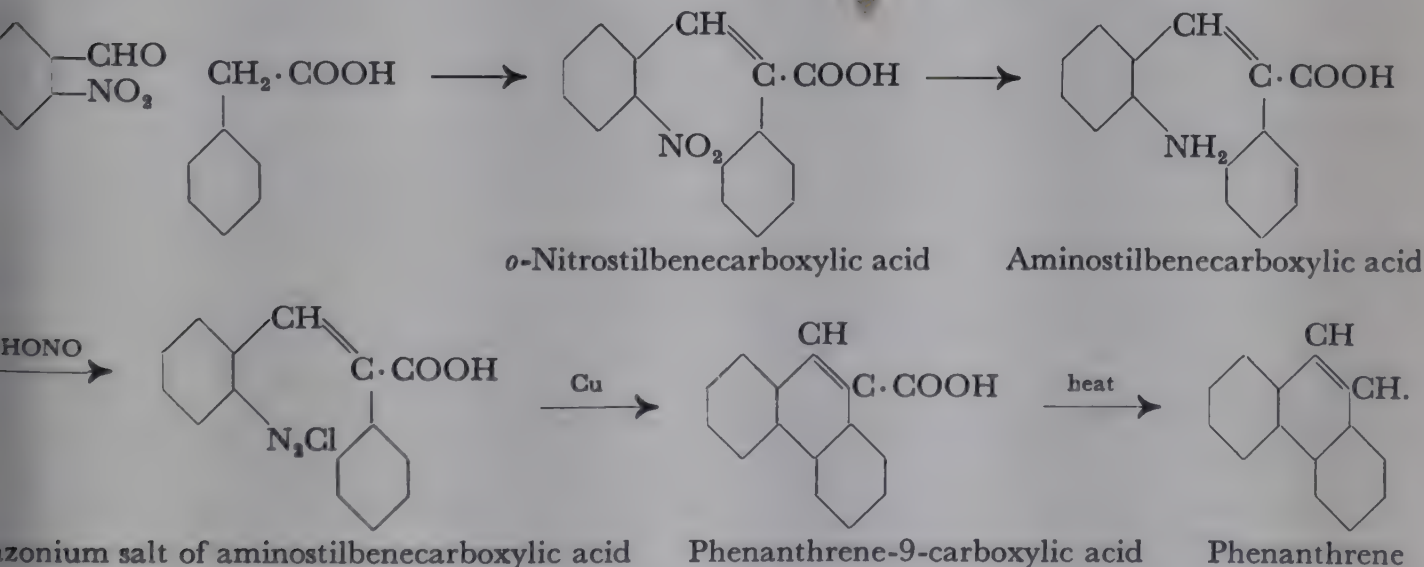
Phenanthrene¹, C₁₄H₁₀



Phenanthrene is also a hydrocarbon which occurs in coal-tar. It seems to be formed as a secondary product in the distillation of coal by pyrogenic condensations. The process can be imitated artificially in different ways, for example, by the passage of biphenyl and ethylene through a red-hot tube:



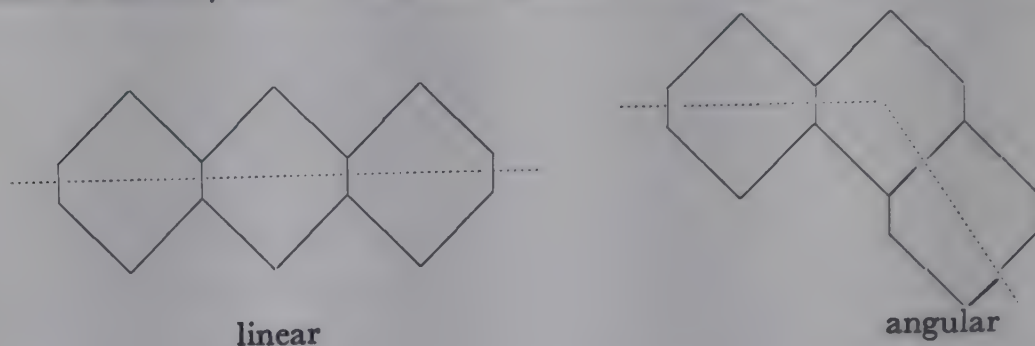
The synthesis of phenanthrene due to Pschorr is general, and is therefore of special importance. Nitrobenzaldehyde and phenylacetic acid are condensed to an *o*-nitrostilbenecarboxylic acid, and this is converted into the corresponding amino-compound, and then, by means of nitrous acid into a "diazonium" salt (see p. 472). By treating this diazonium salt with copper powder ring-closure occurs with elimination of nitrogen, phenanthrene-9-carboxylic acid being formed. When this is heated it decomposes into phenanthrene and carbon dioxide:



Instead of *o*-aminostilbenecarboxylic acid, which is derived from *cis*-stilbene, *o*-amino-*cis*-stilbene itself can also be converted into phenanthrene through the diazo-compound (Ruggli). On the other hand, the reaction is not given with *o*-amino-*trans*-stilbene.

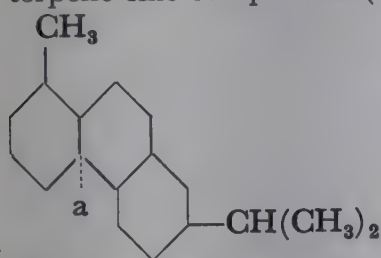
¹ See FIESER and FIESER, *Natural Products Related to Phenanthrene*, 3rd ed. New York, (1949).

Phenanthrene and anthracene are isomerides. Both consist of three benzene rings condensed in the *ortho*-positions. The term "*annulation*" (*annulus* = a little ring) is used for the *ortho*-condensation of six-membered rings, after Hinsberg. If the centres of the individual rings fall on a straight line it is referred to as *linear* annulation, but if the line joining them is bent, as *angular* annulation. Anthracene is linearly annulated, and phenanthrene angularly annulated:



Phenanthrene forms white tablets with a blue fluorescence. Solutions of the compound also fluoresce. It melts at 100° .

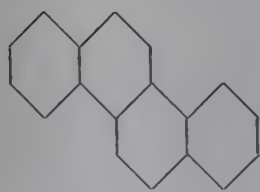
The technical importance of phenanthrene is, at present, small (a few dyes are derived from it). On the other hand, it is of interest that the hydrocarbon is the parent substance of natural products, certain opium alkaloids (morphine, etc.), as well as some terpene-like compounds (fichtelite, abietic acid).



RETENE, $C_{18}H_{18}$, a methyl-isopropyl-phenanthrene occurs in decaying pine wood and in peat deposits. It melts at 98° .

The hydrocarbon is usually accompanied by *fichtelite*, $C_{19}H_{34}$, which is probably a completely hydrogenated retene, containing also a further methyl group at (a).

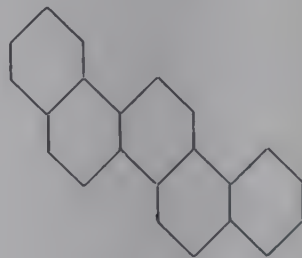
Amongst aromatic hydrocarbons with more than three condensed benzene rings may be mentioned *chrysene*, *pyrene*, and *picene*. Of these, the first two are contained in coal-tar, whilst picene has been obtained from lignite pitch, and the residues from petroleum distillation. They all form characteristic picrates with picric acid. Pyrene is yellow in colour. 3:4-Benzpyrene also occurs in coal-tar and produces cancerous growths; it is one of the substances present in tar which produce cancer. The synthetic hydrocarbon is also active in this connection.



Chrysene $C_{18}H_{12}$
m.p. 250°



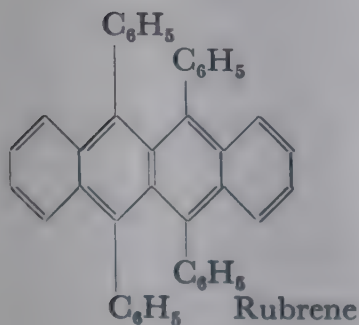
Pyrene $C_{16}H_{10}$
m.p. 149°



Picene $C_{22}H_{14}$
m.p. 364°



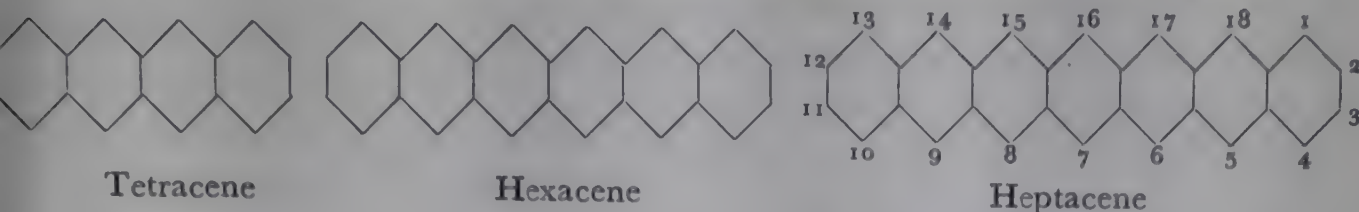
3,4-Benzpyrene
m.p. 177°



Dufraisse has shown that RUBRENE, also known as tetraphenyl-rubene, a red hydrocarbon discovered by C. H. Moureu, is a derivative of *naphthacene*. The compound is the 9:10:11:12-tetraphenyl-naphthacene and has received attention because of its highly unsaturated nature. In the light it combines with oxygen to form a colourless peroxide, which can again be broken down into its components (characteristic for naphthacene derivatives).

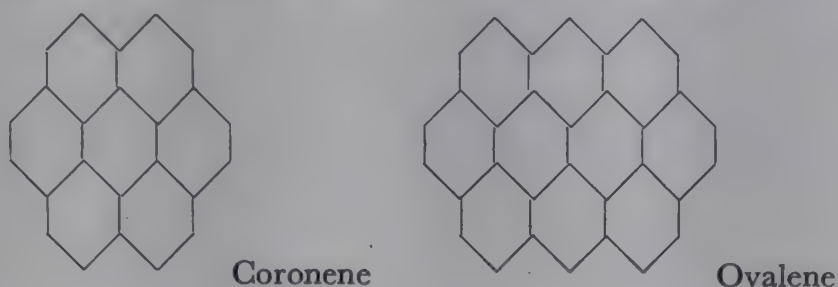
In recent work, particularly by E. Clar and Ch. Marschalk, a number of

higher aromatic hydrocarbons has been prepared containing a larger number of linearly annulated benzene rings, e.g. *tetracene*, *pentacene*, *hexacene*, and *heptacene*:



Some of these hydrocarbons are coloured, owing to the numerous conjugated double bonds present; hexacene is green, and heptacene black-green. They are highly reactive. Thus heptacene, for example, disproportionates at 320° into 6:17-dihydroheptacene and a carbonaceous residue poorer in hydrogen.

On the other hand, hydrocarbons, such as *coronene* and *ovalene*, containing numerous benzene nuclei linked angularly, have also been prepared synthetically.



CHAPTER 24. HALOGEN DERIVATIVES OF AROMATIC HYDROCARBONS

The *chlorination* and *bromination* of aromatic hydrocarbons usually proceeds without difficulty by the direct action of the halogen on the hydrocarbon concerned. The reaction, however, only takes place with the aid of so-called "halogen carriers", i.e. substances which accelerate the reaction catalytically, such as iodine, aluminium chloride, iron, molybdenum chloride, antimony pentachloride, etc. A mixture of iron and iodine (Fierz) is particularly active. If halogen carriers are not used, the chlorine and bromine first dissolve in the benzene and then slowly form addition compounds, $C_6H_6Cl_6$ and $C_6H_6Br_6$ (For the mechanism of the substitution by halogen see p. 387-9).

In the case of aromatic hydrocarbons with side chains the halogen can either substitute in the nucleus or in the side chain according to the reaction conditions. The latter usually takes place if the halogen acts upon the hydrocarbon at a higher temperature, whilst in the cold substitution chiefly takes place in the benzene ring. Light, peroxides, and other compounds can also often act as catalysts for the entrance of halogen into the side chain.

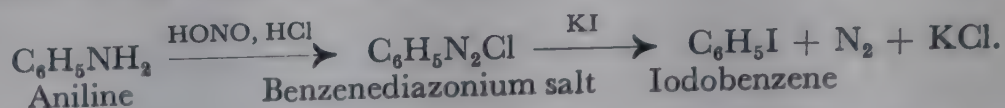
The direct introduction of *iodine* into aromatic hydrocarbons presents greater difficulty, because the hydrogen iodide formed in the reaction partially reduces the iodine compound produced back again to the starting material:



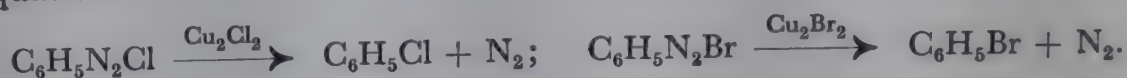
Because of this the reaction proceeds better in the presence of substances

which destroy the hydrogen iodide formed by oxidizing it. Such substances are iodic acid, concentrated sulphuric acid, nitric acid, etc.

Usually, however, the iodine compounds are obtained by indirect methods. A convenient method is the reaction of potassium iodide with diazonium salts (see p. 472). The latter are prepared from primary aromatic amines and nitrous acid, in mineral acid solution. With potassium iodide they react instantaneously with evolution of nitrogen and formation of the iodinated hydrocarbon:



The diazonium salts are also suitable for the preparation of chlorine and bromine compounds. For this purpose they are warmed in aqueous solution with cuprous chloride or cuprous bromide. Decomposition takes place as shown by the equations:



The cuprous halides added take a part in the reaction. They form addition compounds with the diazonium salts, which, on heating, break down to give the desired products. Without the cuprous halides the reaction takes a different course (cf. the diazonium salts, p. 478).

These reactions were discovered by Sandmeyer, and are of great preparative importance.

Aromatic *fluorine* derivatives were formerly difficult to obtain. Recently a good method of preparing them has been found. It consists in warming the diazonium borofluorides which break down in the way shown by the equation: $\text{ArN}_2[\text{BF}_4] \rightarrow \text{ArF} + \text{N}_2 + \text{BF}_3$ (Batz and Schiemann). In certain cases a direct fluorination of the aromatic nucleus is also possible.

The monohalogen derivatives of benzene are liquids with an aromatic smell. They are insoluble in water, but dissolve in organic liquids.

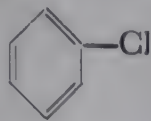
The boiling points increase from fluoro- to iodobenzene:

Fluorobenzene	$\text{C}_6\text{H}_5\text{F}$	b.p. 85°	Bromobenzene	$\text{C}_6\text{H}_5\text{Br}$	b.p. 156°
Chlorobenzene	$\text{C}_6\text{H}_5\text{Cl}$	b.p. 132°	Iodobenzene	$\text{C}_6\text{H}_5\text{I}$	b.p. 188°.

The aliphatic monovalent halogen compounds, the alkyl halides, have been seen to be very reactive compounds, of which the halogen atoms are mobile and can enter into replacement reactions of all kinds. Hence these substances play an important part as the starting point for the preparation of other compounds with monovalent functions.

The aromatic halogen derivatives in which the halogen is attached to the benzene nucleus, are different in nature. The halogen is firmly held and can usually only be replaced at very high temperatures. Chlorobenzene and bromobenzene react with ammonia only when heated with it to 180°–200° in autoclaves, in the presence of copper salts or copper powder. Concentrated aqueous solutions of caustic alkalis only remove the chlorine from chlorobenzene when heated to a temperature of about 300°. The linking of the halogen to the aromatic ring is therefore evidently much stronger than in the molecule of a saturated hydrocarbon. We should recall, however, that there are halogen atoms linked to aliphatic radicals which are also very difficult to remove; they are those which are linked to a carbon united with another by a double bond (see p. 77), e.g. the chlorine in

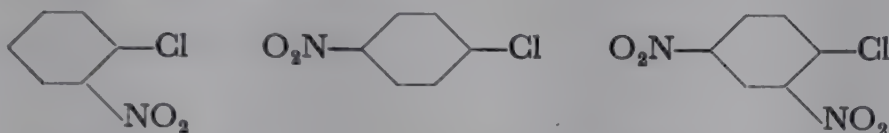
$\text{CH}_3\text{CH}=\text{CHCl}$. The halogen attached as a substituent to the benzene ring is also, without doubt, attached to a carbon atom which is not fully saturated; indeed, on the basis of Kekulé's benzene formula it can be considered as being attached to a carbon linked by a double bond:



From this point of view the inertness of the aromatic halogen derivatives is less surprising. It has analogies in the aliphatic series.

This inertia of chloro- and bromobenzene is, rather unexpectedly, not manifested towards magnesium. They combine with this metal in the presence of ether to form phenylmagnesium chloride and bromide, respectively, which possess the normal properties of Grignard reagents.

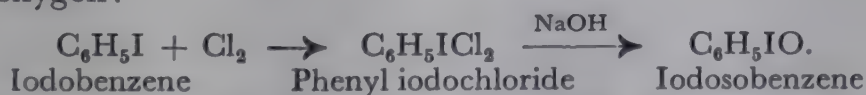
There is another case where the halogen atom linked to the aromatic nucleus is mobile, and that is when certain "negative" substituents, such as $-\text{NO}_2$, $-\text{CN}$, $-\text{COOH}$, are in the *ortho*- or *para*-positions with respect to it. It is a rule throughout the whole aromatic series that such "negative" substituents activate groups in the *ortho*- and *para*-positions and make them mobile. In *o*-nitrochlorobenzene, *p*-nitrochlorobenzene, and *o*, *p*-dinitrochlorobenzene:



the chlorine can, therefore, be substituted by $-\text{OH}$ or $-\text{NH}_2$ much more readily than in chlorobenzene itself. The accumulation of nitro-groups in the *ortho*- and *para*-positions with respect to chlorine increases the reactivity of the latter particularly strongly.

Occasionally a nitro-group in the *meta*-position can increase the reactivity of the halogen atom in certain reactions. Thus, *o*-, *m*-, and *p*-nitrochlorobenzene react in alcohol with alkali sulphites forming salts of nitrobenzenesulphonic acids. The velocity of the reaction is approximately the same for all three nitrochlorobenzenes, but is greatest for the *m*-compound.

The iodine atom in aromatic iodine compounds may, under certain conditions be endowed with a higher valency.¹ Thus, if chlorine reacts with iodobenzene and analogous substances in an indifferent solvent (e.g. chloroform), one molecule of chlorine adds on to the iodine atom. *Phenyl iodochloride* is formed, which crystallizes in yellow needles. (Willgerodt). On treatment with excess of aqueous caustic alkali this is converted into iodosobenzene, in which the chlorine has been replaced by oxygen:



As regards the structure of phenyl iodochloride, it can be considered as phenyl-chloroiodonium chloride according to the formula (a):

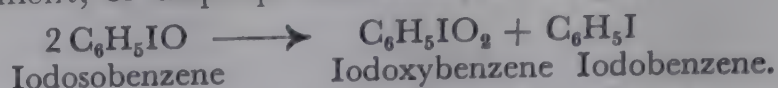


In this case we have in iodosobenzene an analogous compound to the amine

¹ See C. WILLGERODT, *Die organischen Verbindungen mit mehrwertigem Jod*, Stuttgart, (1914).

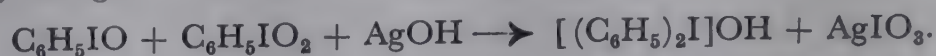
oxides (see p. 126), sulphoxides (see p. 126), and similar compounds, in which the oxygen is linked by a "semipolar" bond, as shown in the formula (b).

Iodosobenzene, which can also be obtained by the action of ozone or peracetic acid on iodobenzene, is a yellow amorphous compound which explodes on heating to 210°. It is slowly converted even at ordinary temperature, and more rapidly on heating, into a mixture of *iodoxybenzene* and *iodobenzene*. There is thus an intramolecular displacement, or disproportionation, of oxygen:

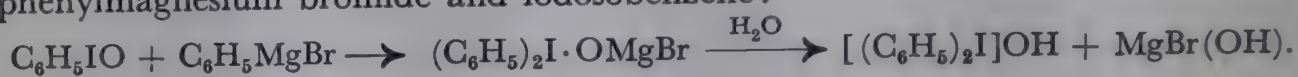


Iodoxybenzene, which can also be obtained by oxidation of iodobenzene with perbenzoic acid, crystallizes in needles. On heating to about 230° it decomposes with explosive violence.

The treatment of an equimolecular mixture of iodosobenzene and iodoxybenzene with water and silver oxide gives rise to characteristic bases, the *iodonium bases*, in which the iodine plays a similar part to the nitrogen in ammonium compounds, being here coordinatively divalent:



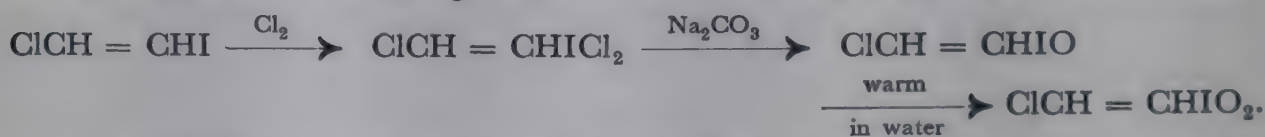
Another way of preparing these substances depends on the reaction between phenylmagnesium bromide and iodosobenzene:



The diphenyliodonium hydroxides are strong bases, comparable with the quaternary ammonium and the sulphonium bases. They precipitate metal hydroxides from solutions of metal salts, and combine with mineral acids to give stable salts. In the salt with hydriodic acid, diphenyliodonium iodide, two types of iodine atom must be distinguished, one of which is non-ionic, and which is attached to the two phenyl groups, and the other ionic:

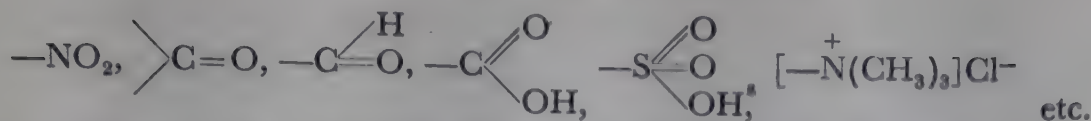


Iodochlorides, iodoso and iodoxy compounds are, however also known in the aliphatic series (e.g. CH_3ICl_2 , decomposing at -28° ; $\text{C}_2\text{H}_5\text{ICl}_2$), but they are in general much more unstable than the corresponding aromatic compounds, and can often only be isolated at very low temperatures. Those in which the iodine atom is attached to a carbon atom linked with a double bond, e.g. 1-chloro-2-iodoethylene, are more stable (Thiele):



POLYSUBSTITUTED HALOGEN DERIVATIVES OF BENZENE can be prepared by the direct action of chlorine or bromine in the presence of halogen carriers; ferric chloride is a suitable catalyst. The second chlorine atom goes principally into the *p*-position with respect to the first. In addition, a good deal of *ortho*-dichlorobenzene is formed but very little of the *meta*-compound.

When new substituents are introduced into an already substituted benzene nucleus, they cannot, as a rule, enter any desired position. The positions they take up are determined by the groups already present; these "direct" the incoming groups to definite positions. Two classes of substituents may be distinguished, those which direct an incoming substituent chiefly into the *ortho*- and *para*-positions, and those which are *meta*-directing. To the first class belong Cl, Br, I, CH_3 , $\text{C}_n\text{H}_{2n+1}$, OH, NH_2 ; and to the second class



It will be noticed that the members of the latter class very often have double bonds, whereas substituents of the first class are generally saturated. The unsaturated, negatively substituted vinyl group $-\text{CH}=\text{CHX}$, however, also belongs to the *ortho-para* directing substituents. The rules of substitution in the benzene nucleus have been thoroughly studied particularly by Holleman.

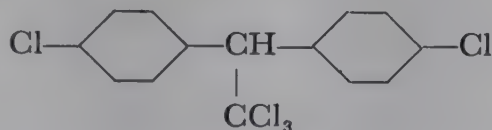
The boundaries between these two groups are not at all sharp. Often all three possible isomerides are formed when disubstitution occurs, as, for example, in the above-mentioned chlorination of benzene. However, one of the three compounds (in our case the *meta*-compound) is formed in much smaller quantity than the others.

Moreover, the above-mentioned rules only hold at relatively low temperatures. Wibaut has shown that when chlorobenzene is chlorinated in the vapour phase at 500–600° chiefly *meta*-dichlorobenzene is formed; in this temperature range the chlorine exerts a *meta*-directing influence. Similar anomalies are observed in bromination. Below 400° *ortho-para* substitution of bromine in bromo- and chlorobenzene predominates, but above 450° substitution occurs in the *meta*-position. Contact catalysts (e.g. ferric bromide) can also alter the relative amounts of the reaction products.

Stronger chlorination of benzene leads first to 1:2:4-trichlorobenzene, which is also produced from all three isomeric dichlorobenzenes, and then through the various stages of chlorination to hexachlorobenzene, C_6Cl_6 (Julin's carbon chloride).

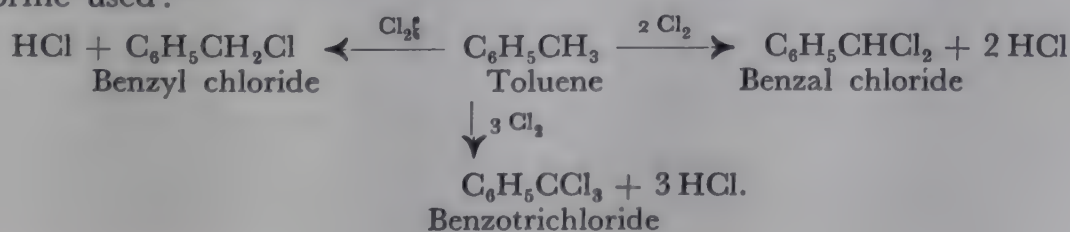
	b.p.	m.p.		b.p.	m.p.
<i>o</i> -Dichlorobenzene	179°	—17.6°	1:2:4-Trichlorobenzene . .	231°	16.6°
<i>m</i> -Dichlorobenzene	172°	—24.8°	1:3:5-Trichlorobenzene . .	208°	53°
<i>p</i> -Dichlorobenzene	173°	53°	Hexachlorobenzene	326°	227°

A polychloro-derivative of diphenyl-methyl-methane, *pp'*-dichlorodiphenyl-[trichloromethyl]-methane



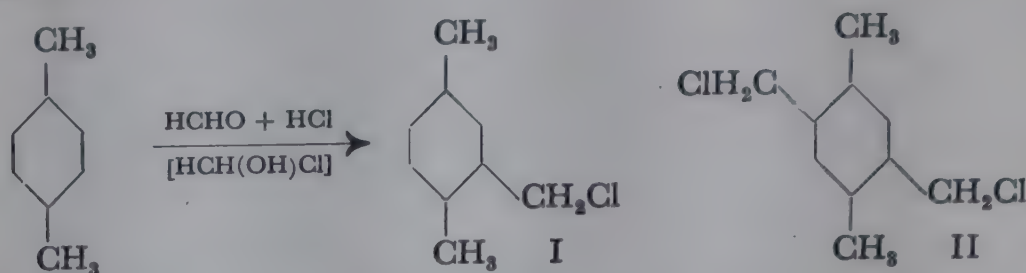
has proved to be an extremely effective means of fighting various animal pests in plants, as well as gnats, flies, lice, and hence against the diseases they transmit (malaria, typhoid fever, etc.). It is known by the trade names "Gesarol", "Neocid" and "D.D.T." The compound is obtained by condensation of chloral with 2 moles of chlorobenzene, and has been known for some time. Its strong insecticidal properties (it acts as a contact poison) were discovered quite recently by chemists of the J. R. Geigy, A. G. chemical works, Basel, Switzerland.

Benzene derivatives substituted with halogen in the side chain are formed by chlorination or bromination of the homologues of benzene at higher temperatures. If, for example, chlorine is passed into boiling toluene, benzyl chloride, benzal chloride, or benzotrichloride is formed, according to the quantity of chlorine used:



Catalysts (FeCl_3 , AlCl_3 , etc.) must not be used for this type of reaction, since they bring about substitution in the nucleus. On the other hand, sunlight favours the entrance of chlorine and bromine into the side chain.

Many aromatic hydrocarbons react with formaldehyde and hydrogen chloride forming chloromethyl derivatives. Thus from *p*-xylene and $\text{CH}_2\text{O} + \text{HCl}$, the chloromethyl derivative I is formed first, and on repeating the process, the compound II:



Halogen atoms linked in the side chain of an aromatic compound are just as reactive, and enter into double decomposition reactions just as well as those of the alkyl halides. It is therefore obvious that the diminished reactivity of the chlorine atoms in aromatic compounds is not due to the presence of the benzene nucleus itself, but to their *special position in the benzene nucleus*. If the chlorine is in the side chain it is reactive.

Benzyl chloride, benzyl bromide, and particularly benzyl iodide have a pungent smell, and affect the mucous membranes, the latter compound so powerfully that work with it is difficult.

		b.p.	m.p.			b.p.	m.p.
$\text{C}_6\text{H}_5\text{CH}_2\text{Cl}$	Benzyl chloride	179°	—39°	$\text{C}_6\text{H}_5\text{CHCl}_2$	Benzal chloride	205°	—17°
$\text{C}_6\text{H}_5\text{CH}_2\text{Br}$	Benzyl bromide	198°	—3.8°	$\text{C}_6\text{H}_5\text{CCl}_3$	Benzotrichloride	221°	—4.7°
$\text{C}_6\text{H}_5\text{CH}_2\text{I}$	Benzyl iodide	—	24°				

CHAPTER 25

NITRO-COMPOUNDS OF AROMATIC HYDROCARBONS

The *aromatic* nitro-compounds are of much greater technical and preparative importance than those of the aliphatic series. The reason for this lies in their greater ease of preparation. Whilst in the preparation of aliphatic nitro-compounds (q.v.) it is necessary to use the action of nitrites on alkylating agents, in the aromatic series the corresponding substances are prepared by direct nitration of the hydrocarbons, i.e. by treating them with concentrated nitric acid.

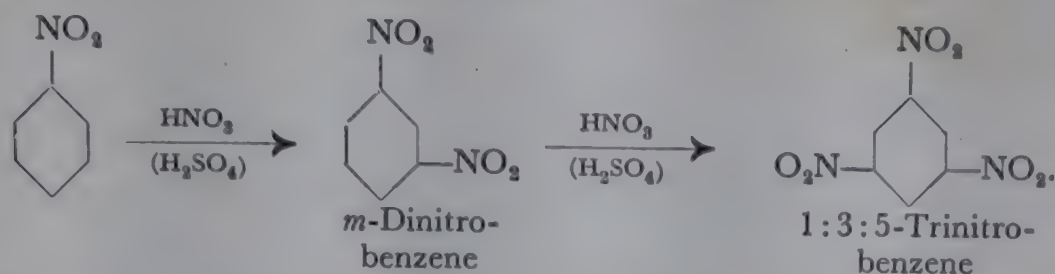
The introduction of the first nitro-group into the benzene nucleus is readily accomplished by means of concentrated nitric acid. Usually, however, a mixture of nitric and concentrated sulphuric acids is used (so-called nitrating mixture). The sulphuric acid removes the water produced during the nitration and thus the reaction occurs more easily:



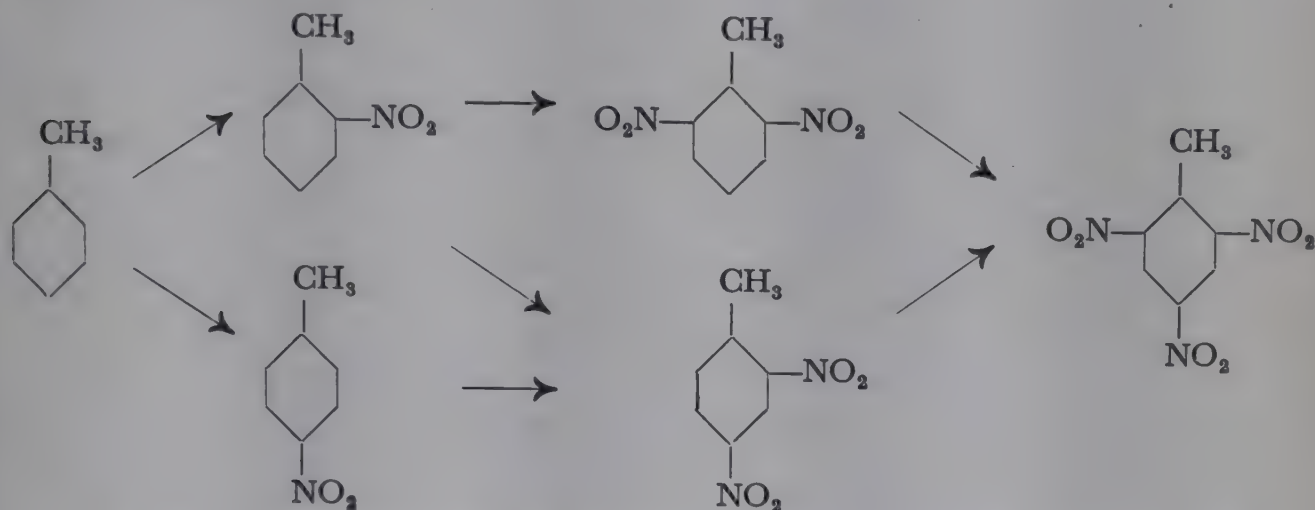
If it is required to introduce more than one nitro-group into the benzene nucleus, it is necessary to use a mixture of concentrated sulphuric acid and fuming

nitric acid. As a *meta*-directing substituent, the first nitro-group directs a second entering nitro-group chiefly into the *meta*-position. In addition to much *m*-dinitrobenzene, however, there is also a small amount of the *ortho*-compound, and traces of the *para*-isomeride.

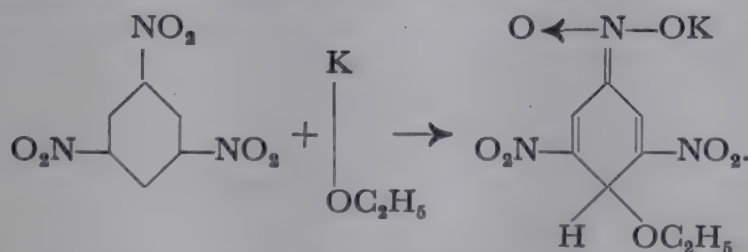
Further nitration converts *m*-dinitrobenzene finally into 1:3:5-trinitrobenzene:



The homologues of benzene (toluene, xylene) are more readily nitrated than benzene itself. From toluene the *ortho*- and *para*-nitrotoluenes (the *ortho*-compound in somewhat greater yield) are chiefly obtained. *m*-Nitrotoluene is found in the reaction mixture in only very small quantities. On further nitration the *ortho*- and *para*-compounds are converted into dinitrotoluenes, and finally into 2:4:6-trinitrotoluene ("T.N.T."):



In the nitro-compounds of aromatic hydrocarbons the nitro-groups are attached to carbon atoms which have no hydrogen atom also attached. They are therefore comparable with the tertiary nitro-compounds of the aliphatic series (see p. 138). Like these, the aromatic nitro-compounds are not capable of forming alkali salts, since transformation into an *aci*-form is not possible. Aromatic nitro-compounds therefore do not dissolve in alkalis. On the other hand, some of them can *add on* the alkali alcoholates. Coloured salts are thus formed, of which the probable constitution is indicated by the following formula:



Although the nitro-group is a "negative" substituent, nitrobenzene can combine with concentrated sulphuric acid to form a well-defined, crystalline sulphate, $\text{C}_6\text{H}_5\text{NO}_2 \cdot \text{H}_2\text{SO}_4$ (m.p. 111°), which has a salt-like character (Cherbuliez).

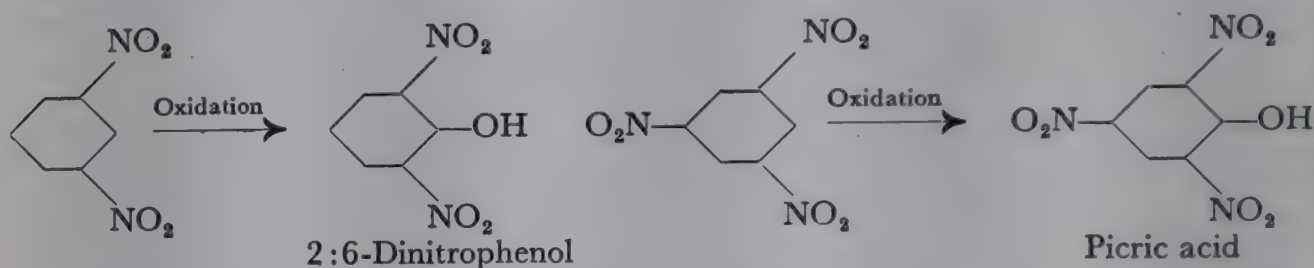
The fact that nitrobenzene increases the conductivity of concentrated sulphuric acid probably depends on the formation of this compound.

Also in other cases, there is a pronounced tendency amongst the nitro-compounds, especially those with more than one nitro-group, to form addition compounds. Thus *s*-trinitrobenzene combines with unsaturated and aromatic hydrocarbons, such as stilbene (see p. 403) and hexamethylbenzene, to give intensely coloured double compounds:



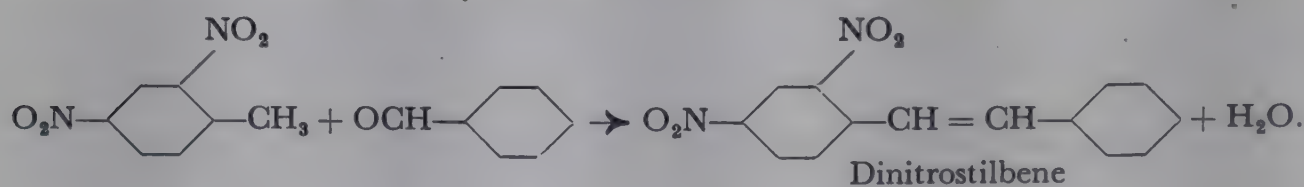
The nitro-group in aromatic nitro-compounds is able to activate the hydrogen atoms of the benzene nucleus which lie in the *ortho*- and *para*-positions with respect to it, as well as other substituents in these positions. Numerous examples can be given:

(a) Whilst the hydroxyl group cannot be directly introduced by oxidation processes into benzene or nitrobenzene in a satisfactory manner, such a reaction is readily carried out with *m*-dinitrobenzene, and even better with *s*-trinitrobenzene:

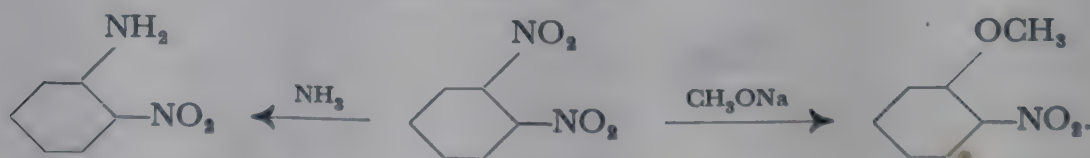


(b) The mobility of halogen atoms in the nucleus under the influence of *ortho*- or *para*-nitro-groups has been referred to in the previous chapter.

(c) Whilst benzaldehyde will not condense with toluene to give stilbene, the hydrogen atoms of the methyl group of *o p*-dinitrotoluene are so mobile that in this case the reaction with benzaldehyde readily takes place. Sodium ethylate is used as condensing agent:



(d) The activating effect of a nitro-group extends to other nitro-groups in the *ortho*- or *para*-positions with respect to the first. Nitrobenzene does not react when heated with either ammonia or sodium alcoholate, but *ortho*-dinitrobenzene or the *para*-isomeride (not the *meta*-compound) readily react, a nitro-group being replaced by $-\text{NH}_2$ or $-\text{OCH}_3$, respectively:

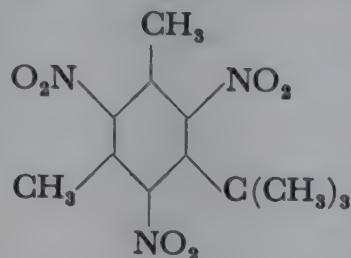


On the other hand, it is surprising to find that on boiling *s*-trinitrobenzene with sodium alcoholates, one of the *meta*-nitro groups is replaced by the alkoxy radical.

NITROBENZENE, OIL OF MIRBANE, is a strongly refracting liquid with a faint yellow colour. It has a strong smell reminiscent of bitter almonds. It is poisonous. It is used in large quantities for the manufacture of aniline (see p. 454). It also finds a limited application in perfumery (for scenting soaps) and as an oxidizing agent (see preparation of fuchsine and quinoline).

Of the **NITROTOLUENES**, the *ortho*- and *para*-compounds are used as the starting points in the manufacture of dyes (see the toluidines). *s*-Trinitrotoluene ("T.N.T.") is one of the most important explosives (used for filling grenades and for blasting purposes).

ARTIFICIAL MUSK. Polynitro-derivatives of aromatic hydrocarbons with a tertiary butyl group are characterized by a strong smell reminiscent of musk, and are therefore used in perfumery. "*Xylene musk*" must be specially mentioned:

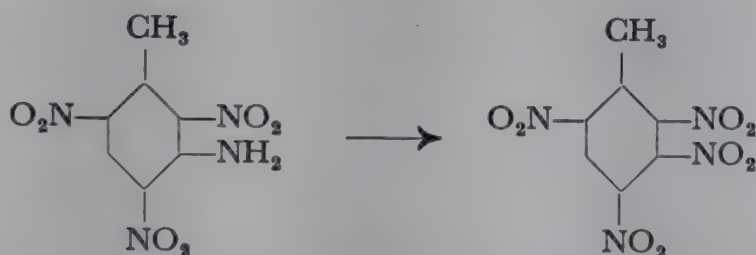


It is prepared by nitrating *m*-tert-butyl-*m*-xylene; m.p. 113°.

"Toluene musk" (CH_3 , $\text{C}(\text{CH}_3)_3$, NO_2 , NO_2 , NO_2 = 1, 3, 2, 4, 6) and "*Ambrette musk*" ($\text{C}_6\text{H}(\text{CH}_3)(\text{OCH}_3)[\text{C}(\text{CH}_3)_3]$ (NO_2)₂ = 1, 5, 2, 4, 6) (m.p. 85°) have a similar smell.

	m.p.	b.p.		m.p.	b.p.
Nitrobenzene	5.7°	210.8°	<i>o</i> -Nitrotoluene	−9.3°	218°
1:2-Dinitrobenzene	116°	319°	<i>m</i> -Nitrotoluene	+16°	230°
1:3-Dinitrobenzene	90.8°	302.8°	<i>p</i> -Nitrotoluene	+51°	234°
1:4-Dinitrobenzene	171–172°	299°	2:4-Dinitrotoluene	70°	—
1:3:5-Trinitrobenzene	121–122°	—	2:4:6-Trinitrotoluene	81.5°	—

Aromatic nitro-compounds with more than three nitro-groups in the benzene nucleus are often obtained by indirect methods. Thus, aromatic trinitroamines are oxidized by potassium persulphate in concentrated sulphuric acid to tetranitrobenzene and its derivatives:



Such tetranitro-compounds are explosive. They are relatively unstable, and are also decomposed by water, especially on heating.

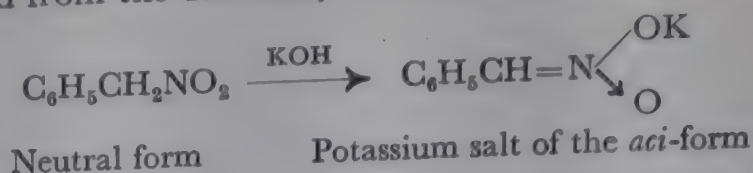
Nitro-compounds with the nitro-group in the side chain. Compounds of this type are prepared by the same methods as are used for the aliphatic nitro-compounds. Thus, the prototype of the whole series, *phenylnitromethane*, is made from benzyl chloride and silver nitrite:



The fact that this compound is a true nitro-compound and not a nitrite is shown by its reduction to an amine (benzylamine).

Phenylnitromethane has the characteristic properties of the primary aliphatic

nitro-compounds. It is itself neutral, and dissolves in alkalis with formation of a neutral salt, derived from the *aci*-form, nitronic acid form, of the substance:



The compound is thus an iso-acid (for pseudo-acids and *aci*-forms see p. 139). Whilst it has not yet been possible to obtain the free *aci*-forms of the aliphatic nitro-compounds in the pure state, that of phenylnitromethane is more stable, and can be isolated. Ordinary phenylnitromethane, the neutral form, is a liquid (b.p. 225°–227°). If, however, the compound is liberated from its sodium salt by the action of the calculated quantity of mineral acid, the *aci*-form crystallizes out (m.p. 84°). It is, however, not very stable, and rearranges within a few hours into the ordinary form again. The *aci*-form of phenylnitromethane being an acid conducts the electric current like an acid, and gives a coloured salt with ferric chloride. The liquid form does not conduct, and does not give the reaction with ferric chloride.

Neutral and *aci*-forms of phenylnitromethanes substituted in the nucleus, e.g. *p*-bromophenyl-nitromethane, $\text{BrC}_6\text{H}_4\text{CH}_2\text{NO}_2$, or *m*-nitrophenyl-nitromethane, $\text{O}_2\text{NC}_6\text{H}_4\text{CH}_2\text{NO}_2$, have also been isolated.

CHAPTER 26

NITROSO- AND HYDROXYLAMINE DERIVATIVES OF AROMATIC HYDROCARBONS

The reduction of aromatic nitro-compounds, which ultimately gives amines, proceeds through various intermediate stages of which the nature varies with the type of reducing agent used. In weakly acid solution, *nitroso-compounds* and *hydroxylamine derivatives* are intermediate products of the reaction. These will be briefly considered here, whilst the amines and other reduction products will be dealt with in later chapters.

Nitroso-compounds. These are formed, as mentioned above, by mild reduction of nitro-compounds in weakly acid or neutral solution. This can be effected by electrolytic methods, or by means of zinc dust and water (Bamberger, Gattermann, Elbs):



For the preparation of nitrosobenzene it is, however, more practicable to use the reverse process, the oxidation of aniline. This is most conveniently carried out with permonosulphuric acid (Caro):



Phenylhydroxylamine, $\text{C}_6\text{H}_5\text{NHOH}$, is formed as an intermediate product. This too can be used for the preparation of nitrosobenzene (e.g. by oxidation with potassium dichromate and sulphuric acid).

NITROSOBENZENE (Bamberger) is *green* in solution, and when molten,

and in this form is monomolecular. The solid compound forms *colourless*, easily volatile needles. They are a bimolecular form of nitrosobenzene. Note that here again, association is accompanied by a diminution in intensity of colour.

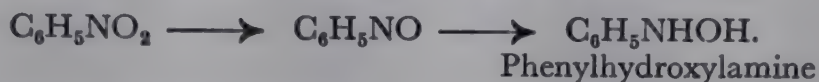
Nitrosobenzene suffers another kind of polymerization under the action of concentrated sulphuric acid. By a process which is comparable with the aldol condensation, nitrosodiphenyl-hydroxylamine is produced:



Nitrosobenzene can easily condense with amines, reactive methylene compounds, etc., by means of the nitroso-group.

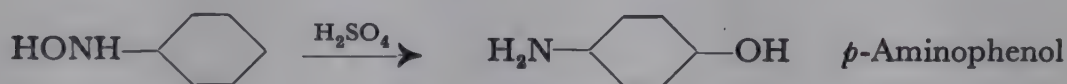
These condensation products will be more fully dealt with elsewhere.

Hydroxylamine derivatives. The aromatic derivatives of hydroxylamine are formed by the neutral reduction of nitro-compounds, or nitroso-compounds. The reducing agents used are aluminium amalgam and water, ammonium chloride and zinc dust, or hydrogen sulphide in the cold:



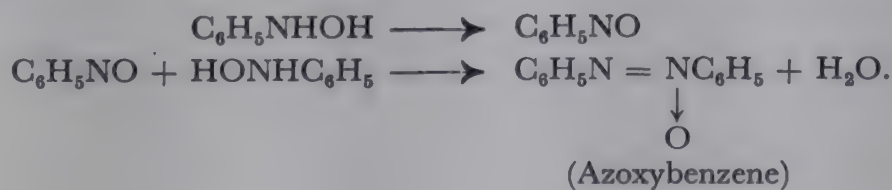
A less suitable method is the oxidation of primary aromatic amines by means of permonosulphuric acid; it is likely to go past the phenylhydroxylamine stage and give nitrosobenzene.

Phenylhydroxylamine (Bamberger) forms colourless needles with a silky lustre, which melt at 81° . It is a strong base, giving stable salts with acids. It isomerizes when treated with concentrated sulphuric acid giving *p*-aminophenol:



This important reaction is used in the preparation of *p*-aminophenol (see p. 468).

Phenylhydroxylamine, like other hydroxylamine derivatives, is readily acted upon by oxidizing agents. It reduces Fehling's solution and silver salts, and in aqueous solution is fairly rapidly oxidized by atmospheric oxygen to azoxybenzene. The latter is the condensation product of unchanged phenylhydroxylamine with nitrosobenzene formed by oxidation:



CHAPTER 27. AROMATIC SULPHONIC ACIDS AND THEIR REDUCTION PRODUCTS

In the aliphatic series the sulphonic acids play only a subordinate part (see p. 123); they are too difficult to prepare to allow of their more general use. It is quite a different matter with their aromatic analogues, which can be easily obtained by the action of concentrated sulphuric acid on aromatic hydrocarbons (the so-called *process of sulphonation*), and which are useful starting substances for further syntheses. When, however, all the nuclear hydrogen atoms of benzene or its derivatives are substituted, sulphonation will no longer take place.

When benzene is sulphonated the monosulphonic acid is first formed:



If the reaction is carried out in the cold, a great excess of sulphuric acid is necessary, since the water produced in the reaction dilutes the acid and the latter becomes ineffective if its strength falls below 65 %. This difficulty is overcome by carrying out the reaction at higher temperatures (about 170–180°), because then the water formed evaporates and the concentration of the acid is maintained.

The aromatic sulphonic acids may be separated from the excess of sulphuric acid either by means of the barium salts (those of the sulphonic acids being readily soluble in water), or the sulphuric acid solution, diluted with water, is saturated with common salt, which throws out of solution the crystalline sodium salt of the sulphonic acid ("salting out").

By more energetic sulphonation of benzene (heating with fuming sulphuric acid), di- and trisulphonic acids can be obtained. More than three sulphonate groups cannot be introduced into the benzene nucleus in this way. Certain metal salts, particularly silver sulphate and mercury sulphate, accelerate the process. The *meta*- and *para*-disulphonic acids are produced together, the former predominating. *o*-Benzenedisulphonic acid is not formed. Prolonged strong heating of *m*-benzenedisulphonic acid with fuming sulphuric acid causes partial isomerization to the *para*-compound; on the other hand, the *para*-compound is partially converted into the *meta* under the same conditions, so that after long heating an equilibrium state is reached.

The homologues of benzene are preferentially sulphonated in the *p*-position:



Some of the *o*-compound is formed at the same time.

The addition of mercury, or better mercury sulphate, can alter the yields of the isomerides considerably. This is a general rule for the sulphonation of benzene derivatives, and is due to the fact that by the action of the mercury, mercury substitution products are formed which then exchange the Hg for the sulphonic acid group.

Naphthalene forms two position-isomeric sulphonic acids, which are formed together by the action of sulphuric acid on naphthalene. A low sulphonation temperature (about 80°) favours the formation of the α -acid, whilst the β -acid is produced at about 160°.

According to the Armstrong rules, in the sulphonation of naphthalene, low temperatures favour substitution in the α -, higher temperatures in the β -position; moreover, the second sulphonate group always enters the yet unsubstituted nucleus, while the third goes

into the *meta*-position relative to the sulphonate group already present. Several di- as well as trisulphonic acids of naphthalene have technical importance (2:6-, 2:7-, 1:5-disulphonic acids, 1:3:5-, 1:3:6-trisulphonic acids).

The aromatic sulphonic acids are crystalline solids, very hygroscopic, deliquescent in moist air, and very soluble in water. They are strong acids and form stable salts with metals, which usually crystallize well. Their alkali-metal salts are readily soluble in water.

It is comparatively easy to replace the sulphonic acid radical by other groups, and the aromatic sulphonic acids are therefore used as starting materials for the preparation of substances with other functional groups. They take the place in the aromatic series of the alkyl halides in the aliphatic series, and their preparative and even technical importance depends to a large extent on this fact.

On fusion with alkalis (caustic soda or caustic potash) they give *phenols*, aromatic hydroxy-compounds:

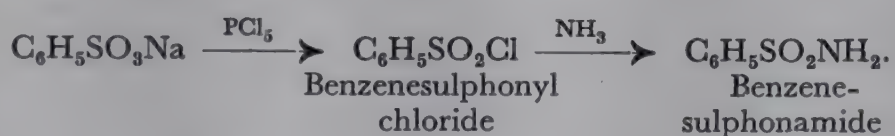


On heating sulphonates with potassium cyanide, aromatic *nitriles* are formed:

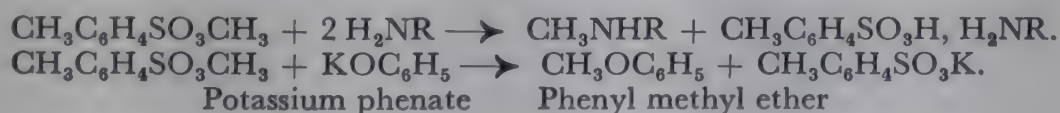


The sulphonic acid group can also be replaced by *hydrogen*, this being best carried out by heating the sulphonic acid with dilute sulphuric acid or phosphoric acid to a high temperature. In some cases much milder treatment will suffice. Thus α -naphthalenesulphonic acid can be reduced in aqueous solution by sodium amalgam to naphthalene even at ordinary temperatures.

Phosphorus pentachloride converts the aromatic sulphonic acids into the comparatively stable *sulphonyl chlorides*, which may be used for the introduction of the arylsulphonic acid radical into other compounds. Some sulphonyl chlorides can be obtained directly and smoothly by the action of chlorosulphonic acid on hydrocarbons. With ammonia they give the arylsulphonamides, which are usually difficultly soluble, and crystallize well, and therefore serve for the characterization of the sulphonic acids:

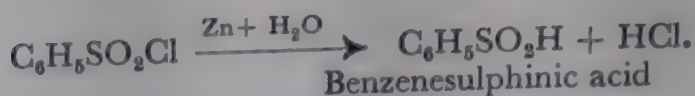


The methyl esters of benzenesulphonic acid, and particularly of *p*-toluenesulphonic acid have become of great practical importance. If they are allowed to act upon amines, or in alkaline solution with alcohols or phenols, they give up their alkyl group to these compounds. They therefore act as methylating agents and are often used for this purpose:



Whilst direct reduction of sulphonic acids is not possible, some of their derivatives, particularly the acid chlorides, can be reduced to lower stages of oxidation. *Sulphinic acids* or *thiophenols* are thus obtained according to the method of reduction.

Sulphinic acids. These are obtained by reduction of arylsulphonyl chlorides with zinc dust and water:

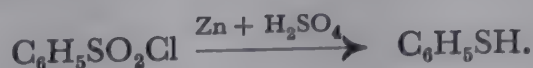


Benzenesulphinic acid has also been obtained by the action of sulphur dioxide and anhydrous aluminium chloride on benzene.

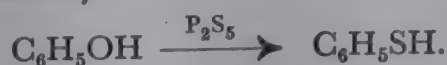
The arylsulphinic acids are solids which crystallize well and are difficultly soluble in cold water. They react acid.

Thiophenols. Aryl-SH. Thiophenols are produced:

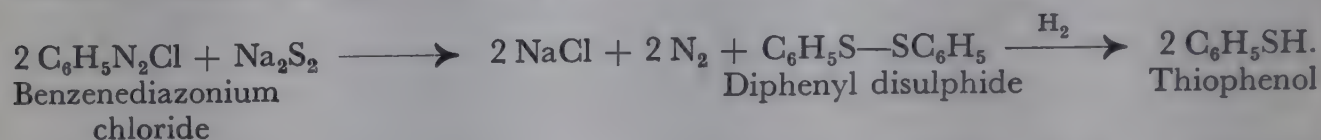
(a) by energetic reduction of the arylsulphonyl chlorides, e.g. with zinc in sulphuric acid solution:



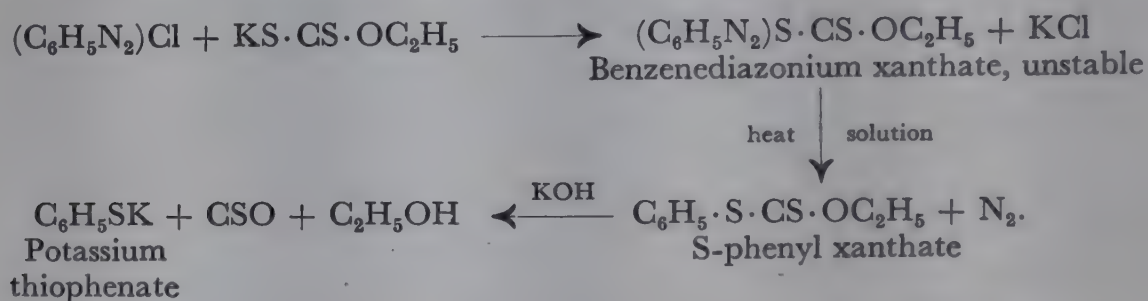
(b) by the action of phosphorus pentasulphide on phenols; this reaction however, proceeds less smoothly:



(c) They are best obtained from diazonium salts (see p. 476) by two different methods. Either the diazonium salt is converted into the aromatic disulphide by means of sodium disulphide, and this is reduced to the thiophenol:



or the benzenediazonium salt is added to potassium xanthate, giving a xanthate ester, which is then decomposed by alkali:



THIOPHENOL is a colourless liquid with a repulsive smell. It boils at 169°. The compound reacts acid, like the aliphatic mercaptans, and forms stable alkali- and heavy-metal salts, the well-crystallized mercury salt being characteristic. Oxidizing agents, even atmospheric oxygen, convert thiophenol into diphenyl disulphide:



Many of the so-called "sulphur dyes" are complex aromatic disulphides (see Ch. 49, section D). Their reduction products, the leuco-compounds, have the nature of thiophenols.

Halogeno- and nitrobenzenesulphonic acids. Chloro- and bromobenzene can be sulphonated by fuming sulphuric acid like benzene. The *p*-sulphonic acids only are obtained. Their properties are analogous to those of benzenesulphonic acid.

Nitrobenzenesulphonic acids are obtained either by sulphonating nitrobenzene, or nitrating benzenesulphonic acid. In the first case the product consists of about 98 per cent of *m*-nitrobenzenesulphonic acid, and 2 per cent of the *p*-compound, whilst nitration of benzenesulphonic acid gives about 50 per cent *meta*-, 35 per cent *ortho*-, and 15 per cent *para*-nitrobenzenesulphonic acid.

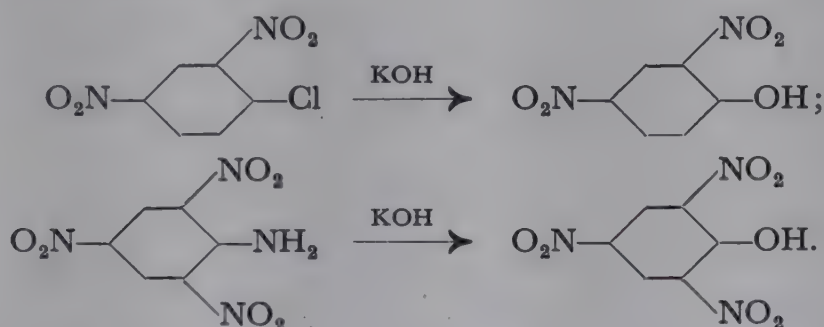
CHAPTER 28. PHENOLS

Monohydric phenols

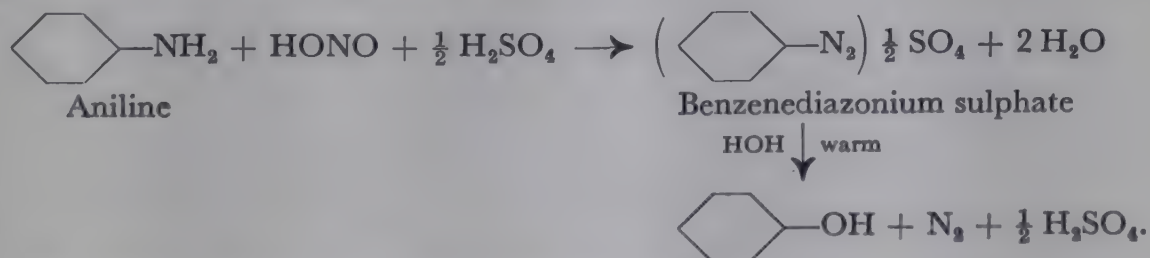
The term *phenol* covers aromatic hydroxy-compounds in which the hydroxyl group is directly linked to the aromatic nucleus. If the hydroxyl group is in a side-chain, the compound is referred to as an *aromatic alcohol*.

Preparation of phenols. 1. Phenols are not very easily obtained in general from *aromatic halogen compounds*, because, as we have seen (p. 414), halogen atoms attached to the nucleus are firmly held. This difficulty has, however, been overcome by heating the phenyl halide with dilute (about 8 per cent) aqueous sodium hydroxide in the presence of copper salts in autoclaves to high temperatures. The yield of phenol is so good that the process is now used technically for the large-scale preparation of phenols.

It has been pointed out in Chapters 24 and 25 that nitro-groups activate substituents in the *ortho*- and *para*-positions, and make them capable of entering into replacement reactions. Halogen atoms, amino- and nitro-groups which are influenced by such nitro-groups, are thus replaced by hydroxyl on warming with aqueous solutions of alkalis, or even on treatment with alkali-metal carbonates. The mobility of these substituents increases with the number of nitro-groups in the *o*- and *p*-positions. Thus, the chlorine in 2:4-dinitro-chlorobenzene is more reactive than that in 2-nitro-chlorobenzene, and in 2:4:6-trinitro-chlorobenzene the mobility is still further increased:



2. Phenols are often prepared from *aromatic primary amines*. These are diazotized by the method described on p. 472, i.e. they are converted into diazonium salts by the action of nitrous acid in hydrochloric acid or sulphuric acid solution. If these are allowed to stand for some time in the acid solution, or if the liquid is warmed, nitrogen is evolved and a phenol is produced:

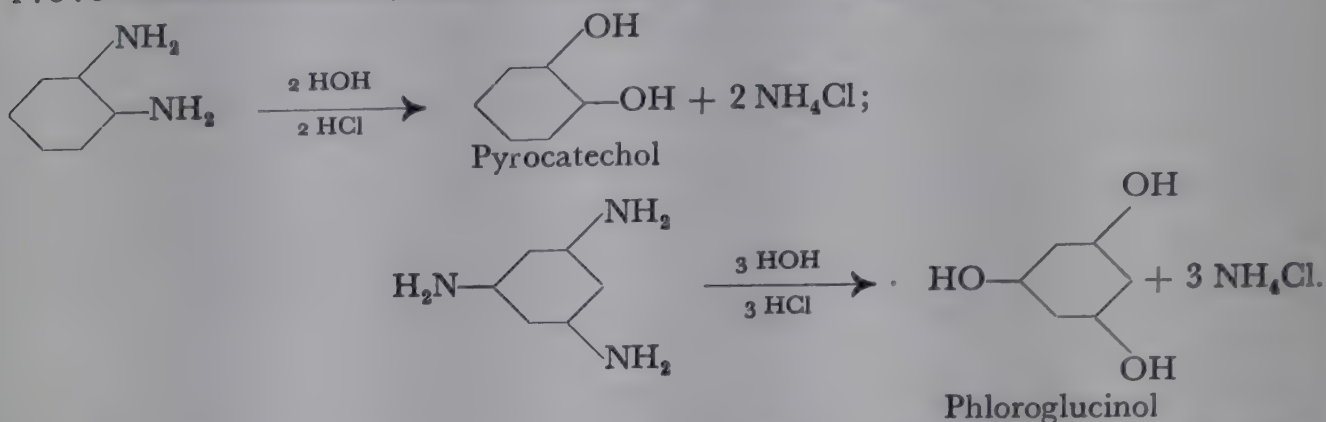


The method often gives excellent results. It corresponds to the conversion of the primary aliphatic amines into primary alcohols (see p. 82) by the action of nitrous acid.

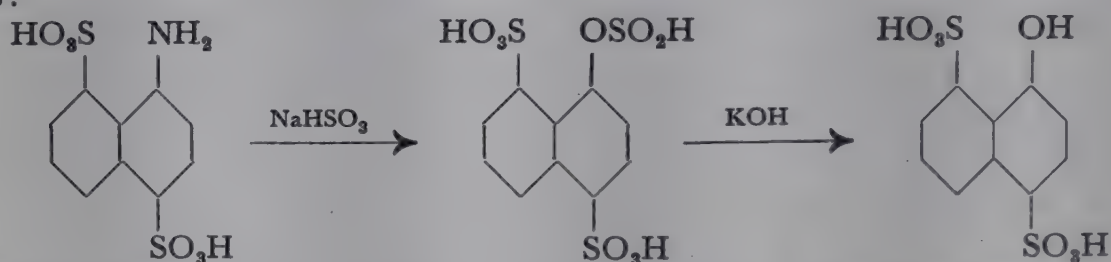
More complex diazonium salts, e.g. those derived from *aminophenols*, do not react so smoothly in this way. In these cases the diazonium salt solution is

allowed to drop into a boiling aqueous solution of copper sulphate, when the hydrolytic decomposition of the diazonium salt into a phenol, nitrogen, and acid takes place normally.

Whilst simple aromatic amines are very stable towards hydrolysis, and their amino-groups, except those activated by the presence of nitro-groups, are not eliminated by boiling with water or alkalis, the direct hydrolysis of aromatic *polyamines* to polyhydric phenols is often successful (J. Meyer). For example *o*-phenylenediamine gives pyrocatechol on long boiling with dilute acids, and 1:3:5-triaminobenzene, under analogous conditions gives phloroglucinol:



The *amines of the naphthalene series*, especially naphthylaminesulphonic acids with the sulphonic acid radical in the *p*-position with respect to the amino-group, are readily converted into phenols by heating with *sodium bisulphite* (Bucherer). The sulphurous ester of the phenol is first formed, which is then decomposed by alkalis:

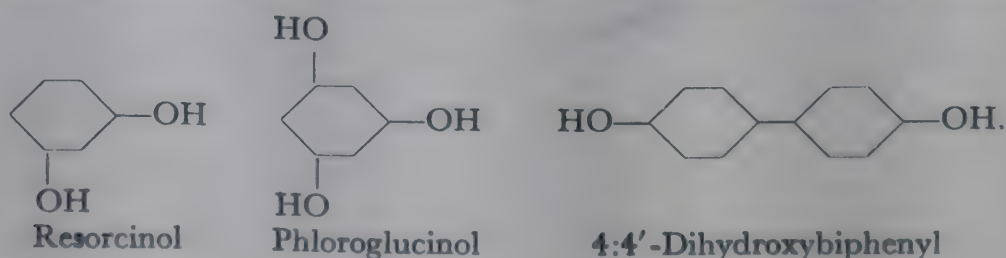


3. One of the most important methods of preparing phenols is the *fusion of the aromatic sulphonic acids with alkalis*. The sulphonic acid radical is thus replaced by hydroxyl:

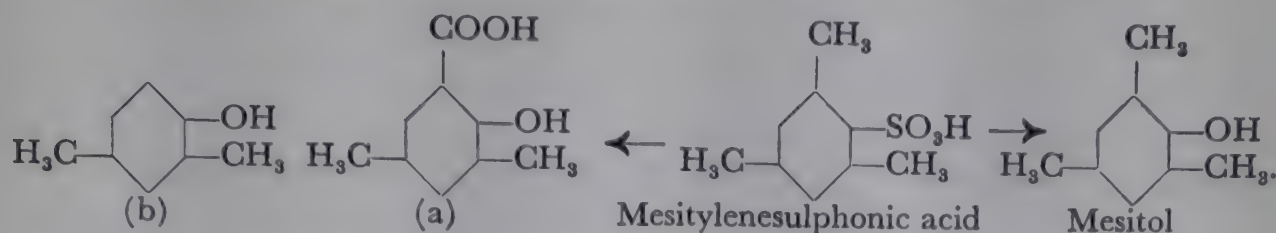


In industry the sodium salts of the acids and sodium hydroxide are generally used. The more expensive caustic potash gives, however, better yields of phenols, and fewer by-products.

The latter are produced largely by oxidation processes. These always occur in an alkali fusion. They can lead either to the introduction of more hydroxyl groups into the nucleus, or to the linking of the benzene nuclei. Thus, when benzenesulphonic acid is fused with alkali, there are produced in addition to the main product, phenol, also resorcinol, phloroglucinol, and 4:4'-dihydroxybiphenyl:



In other cases the alkali fusion of a sulphonic acid is accompanied by oxidation of the side chain. For example, there are obtained from mesitylenesulphonic acid, a carboxylic acid (a), and a xylenol (b) [produced by elimination of carbon dioxide from (a)], in addition to the main product, mesitol:

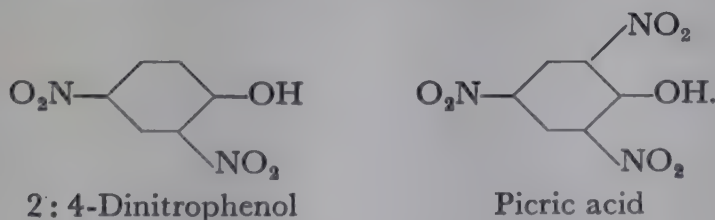


The alkali fusion of the sulphonic acids is not suitable for the determination of constitution. It is often found that rearrangements take place so that the incoming hydroxyl group does not occupy the place vacated by the sulphonic acid radical. Thus not only does *m*-benzenedisulphonic acid give *m*-dihydroxybenzene (resorcinol) on fusion with alkali, but *p*- and *o*-benzenedisulphonic acid also give the same compound, though in small quantities.

Properties of phenols. 1. The phenols are more strongly acid than the alcohols. They dissolve in aqueous solutions of alkalis, and their salts, the *phenates*, are only slightly hydrolysed by water. The aromatic radical therefore increases the acidity of the hydroxyl group. Probably the cause of this phenomenon is the same as that which makes the enolic compounds (q.v.) strongly acidic. In the latter case the increase of acidity compared with the saturated alcohols was ascribed to the position of the hydroxyl group, being attached to a carbon atom linked by a double bond. In the phenols too, the hydroxyl group is attached to an unsaturated carbon atom (according to Kekulé's formula, at a "double bond").

Carbon dioxide reprecipitates the phenols from their aqueous alkali solution. In this way they can be separated from carboxylic acids.

Nitro-groups and other negative substituents (e.g. halogens) increase the acidic character of the phenolic hydroxyl group if they are in the *ortho*- or *para*-position with respect to it. 2:4-Dinitrophenol is a stronger acid than phenol itself, and in 2:4:6-trinitrophenol, or *picric acid*, we have a substance, of which, as its name implies, the acidity approaches, and often exceeds, that of carboxylic acids:



2. Most phenols are fairly readily attacked by oxidizing agents. They react in different ways according to their nature and that of the oxidizing agent. Thus the oxidation of phenol with hydrogen peroxide in the presence of ferrous sulphate gives pyrocatechol, some pyrogallol, and traces of hydroquinone. Dihydric phenols with hydroxyl groups in the *ortho*- and *para*-positions give under suitable conditions *ortho*- and *para*-quinones, and diketo-compounds.

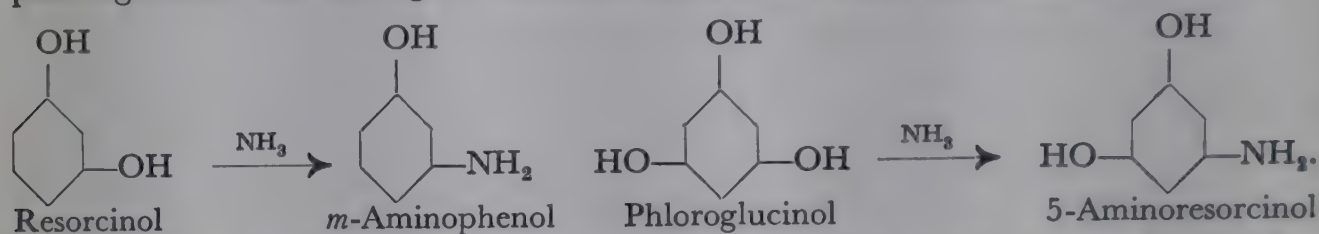
3. Most free phenols give colorations with ferric chloride in neutral, or

weakly acid solution, which are due to the formation of complex iron salts.¹ Red, blue, violet, green, and brown colorations are observed according to the nature of the phenol. These are often used for the qualitative detection of the phenols.

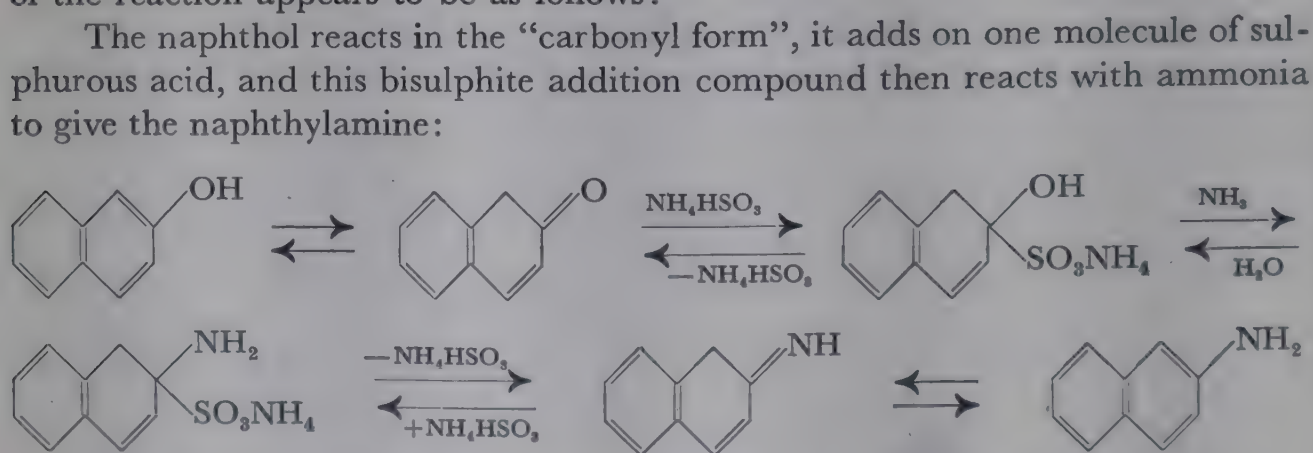
4. Liebermann's reaction. Many phenols give colorations when added to a solution of potassium nitrite in concentrated sulphuric acid. This reaction, discovered by Liebermann, is also occasionally used as a test for a phenol.

5. By distillation with zinc dust, phenols are reduced to hydrocarbons. The method has often been used to find the parent hydrocarbon especially in the case of complex phenols, and so to obtain the first clue to their constitution.

6. Of considerable importance — greater than in the aliphatic series — is the replacement of the hydroxyl group of phenols by amino-groups. In the case of the monohydric phenols there are, however, difficulties. The simplest phenol, C_6H_5OH , gives, only on heating with the double compound of zinc chloride and ammonia to about 300° , considerable quantities of aniline, $C_6H_5NH_2$, and diphenylamine, $C_6H_5NHC_6H_5$. The conversion of the polyhydric phenols into amines proceeds more readily. Resorcinol is converted into *m*-aminophenol on heating with a concentrated aqueous solution of ammonia to 200° , and in the case of phloroglucinol the analogous reaction takes place even on gentle warming:



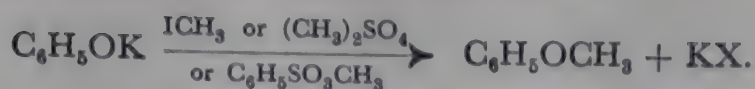
From the practical point of view the replacement of the hydroxyl-group by the amino-group in the naphthalene series is the most important. It is used for the preparation of the naphthylamines from the naphthols, and according to the method of H. T. Bucherer, the reaction is carried out by heating aqueous solutions of ammonium sulphite with naphthols to 100 – 150° in autoclaves. The mechanism of the reaction appears to be as follows:



This formulation shows that the Bucherer reaction is reversible.

7. PHENOLIC ETHERS. The replacement of the hydrogen atom of the phenolic hydroxyl group by an alkyl radical, with the formation of mixed aromatic-aliphatic ethers, can be carried out by the ordinary methods of etherification. The alkali-metal phenates, or their aqueous solutions are warmed with alkyl halides, dialkyl sulphates, or toluene- or benzenesulphonic acid esters:

¹ See R. WEINLAND, *Einführung in die Chemie der Komplexverbindungen*, 2nd ed., Stuttgart, (1924).



The phenolic ethers are very stable, neutral compounds, difficultly soluble in water, and often have a strong smell. They are usually indifferent towards alkalis, but are cleaved by concentrated acids, like the aliphatic ethers. Hydriodic acid is mostly used for this purpose. The fission always takes place in such a manner that the alkyl radical combines with the halogen. One molecule of the phenolic ether thus gives one molecule of CH_3I , $\text{C}_2\text{H}_5\text{I}$, etc. and the quantitative estimation of these alkyl halides can therefore serve for the quantitative determination of the phenolic ether groups (Zeisel's method):



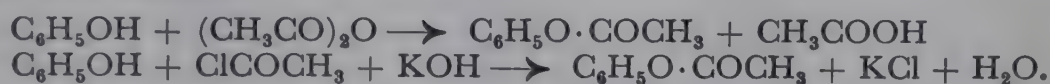
Some phenolic ethers are readily "hydrolysed" by anhydrous aluminium chloride:



A new method of hydrolysis, which can also be used for the methylene ethers of dihydric phenols, is based on the action of sodamide in indifferent solvents (e.g. toluene) on such compounds; another method is based on heating the phenolic ether with pyridine hydrochloride to 200° .

Phenolic ethers, particularly methyl ethers, are very widely spread in nature.


8. PHENOLIC ESTERS. The esterification of phenols is carried out by the same methods as the acylation of aliphatic alcohols. They are treated with acid anhydrides, or with acid chlorides in the presence of some reagent which will retain the acid formed:



The latter process is the more common and is more generally applicable. The process is carried out according to Schotten-Baumann, by adding the acid chloride with shaking to the phenol dissolved in the calculated quantity of aqueous alkali, or by adding equimolecular quantities of alkali and acid chloride together drop by drop to the phenol solution. The esterification takes place particularly readily when aromatic acid chlorides are used. Since the benzoic, anisic, and toluene-sulphonic esters of many phenols are difficultly soluble, and crystallize well, they often serve for the isolation, characterization, and purification of these substances.

From the number of acyl groups entering on acetylation or benzylation, the number of hydroxyl-groups present may be determined.

Nowadays pyridine is frequently preferred to caustic alkalis as an acid-retaining substance in these acylations. It is more moderate in its action, and its use prevents subsequent hydrolysis of the ester formed. The phenol is dissolved in dry pyridine and the required quantity of acid chloride is added at ordinary temperatures. The acylation is complete after some hours, and the ester can then be precipitated by pouring the pyridine solution into water.

Individual monohydric phenols. PHENOL, -OH. The simplest phenol, known simply as phenol, or *carbolic acid*, is found in coal-tar in which it was discovered by Runge in 1834. Its correct composition was given by Laurent (1842). The phenol used in industry is obtained almost exclusively from coal-tar.

The occurrence of phenol as a normal product of metabolism in animal and human urine is noteworthy. It occurs here as a degradation product of tyrosine,

from which it is also formed in the decay of proteins. Benzene is converted to a large extent into phenol in the animal organism.

Phenol can be synthesized by fusing benzenesulphonic acid with alkali (p. 428), and especially from chlorobenzene on heating with aqueous alkalis (p. 414).


Phenol forms colourless, prismatic crystals, which melt at 43° ; b.p. 181° . It has a very intense and characteristic smell. In water at 15° it dissolves to the extent of about 8 per cent but is very readily soluble in aqueous alkalis. Phenol can only be kept for any length of time in the absence of air. In air it gradually becomes coloured red.

The compound is characterized by a number of very sensitive colour reactions. Ferric chloride gives a blue colour. When ammonia and bromine water are added to a solution of phenol, an indigo-blue colour results, which persists for some time. Liebermann's reaction (concentrated sulphuric acid, potassium nitrite, and phenol) gives a blue-green liquid. If the sulphuric acid solution is poured into water the colour becomes red, and on addition of alkali it becomes blue.

When bromine water is added to a solution of phenol an exceedingly difficultly soluble precipitate of $C_6H_2Br_4O$ (2:4:6:6-tetrabromo-*cyclohexadiene*-(1:4)-one-(3) or 2:4:6-tribromophenyl hypobromite, $Br_3C_6H_2OBr$) is formed. It may be used as a test for phenol (though similar precipitates are also given by homologues of phenol).

Phenol is one of the most important and most indispensable substances of the organic heavy chemical industry. It is used for the preparation of numerous dyestuffs, plastics, and artificial tannins. For the manufacture of plastics it is usually condensed with formaldehyde by the action of sulphuric acid. If the phenol is in excess, artificial resins which can be hardened (bakelite, resols) are formed, in which phenol residues are connected by CH_2 -groups in the *o*- and *p*-positions. If an excess of formaldehyde is used, the phenol residues are linked partly by two or three CH_2 -bridges (hardened resins, bakelite C, resites).

Phenol is further used for the synthesis of picric acid (see p. 449). Carboic acid also plays an important part as a disinfectant. Finally, it serves as the starting material for the preparation of many drugs, especially salicylic acid (see p. 535), and its esters [e.g. salol, (see p. 537)], etc.

ANISOLE,  OCH_3 , phenyl methyl ether, is a pleasant smelling liquid, boiling at 153° , and melting at -37° . The compound is formed as a degradation product of anethole (see p. 434), and is most conveniently prepared from phenol, dimethyl sulphate and alkali. It is used as a solvent, and as the starting material for the preparation of derivatives, e.g. *p*-methoxy-acetophenone, a perfume ($CH_3O \cdot C_6H_4 \cdot CO \cdot CH_3$).

PHENETOLE,  OC_2H_5 ; b.p. 172° ; m.p. -33° .

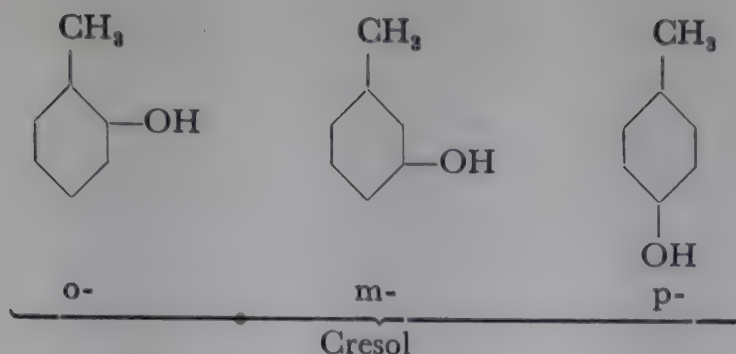
DIPHENYL ETHER, . According to Ullmann this compound

may be prepared from potassium phenate, bromobenzene, and fine copper powder, which are heated together to 210° :



Diphenyl ether is used as a perfume (of geranium odour).

CRESOLS. The three isomeric hydroxytoluenes are called cresols:



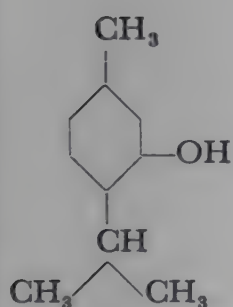
The three compounds occur in the middle-oil fraction of coal-tar. They are usually not separated from each other for technical purposes, though the separation of the mixture is possible. By repeated careful fractionation, *o*-cresol (b.p. 191° , m.p. 30°) may be distilled from the crude product. *m*-Cresol (b.p. 203° , m.p. 4°) and *p*-cresol (b.p. 202° , m.p. 36°) are separated through their sulphonic acids. That of *m*-cresol is broken down on boiling with dilute sulphuric acid at 130° , whilst that derived from *p*-cresol remains unchanged under these conditions.

Chemically pure cresols are frequently prepared from the isomeric aminotoluenes, or toluidines (see p. 457), by diazotization. *p*-Cresol is a product of decay of tyrosine.

The cresols possess an even more powerful disinfectant action than phenol. They are therefore used extensively as disinfectants. Thus "creoline" is an emulsion of cresols, tar oils, and pyridine in soap solution. "Lysol" is a solution of crude cresol in soap (potassium soap from linseed oil fatty acids). *p*-Chloro-*m*-cresol is characterized by powerful disinfectant action, and low toxicity. The use of cresols for impregnating wood, railway sleepers, etc., also depends upon their bactericidal action. They are also used in industry for the manufacture of dyestuffs, perfumes, and explosives.

HIGHER HOMOLOGUES OF PHENOL. Six isomeric *xlenols* are derived from the xylenes; they are contained in part in coal-tar. The phenol derived from mesitylene is *mesitol*, and the hydroxy-derivatives of hemimellitene and pseudocumene are called *hemimellitenols* and *pseudocumenols*.

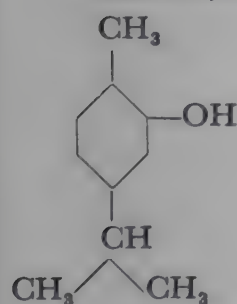
Xylenols:	1 : 2-dimethyl-3-hydroxybenzene,	m.p. 73° , b.p. 213°
1 : 2	" -4- "	" 65° , " 222°
1 : 3	" -2- "	" 49° , " 203°
1 : 3	" -4- "	" 25° , " 209°
1 : 3	" -5- "	" 63° , " 218°
1 : 4	" -2- "	" 75° , " 209°



THYMOL, a hydroxy-derivative of 1-methyl-4-isopropylbenzene (*p*-cymene) is contained in many essential oils, e.g. oil of thyme, and the oil of Ajowan. It is prepared technically from the latter. It is used as an antiseptic in medicine. It forms colourless, hexagonal tables, m.p. 51° , b.p. 232° .

On the degradation of menthone to give thymol, see menthone.

ARISTOL, an iodine derivative of thymol, is used as a substitute for iodoform.



CARVACROL is the second of the two possible phenolic derivatives of *p*-cymene. It differs from thymol in the position of the hydroxyl group.

Carvacrol is found in many essential oils, e.g. in dittander oil and in the oil from *Origanum hirtum*. It is closely related to the camphors, from some of which it can be obtained by simple reactions. It is readily prepared from carvone (see Ch. 54) which isomerizes to carvacrol on heating with formic acid or phosphoric acid.

Carvacrol melts at 0° and boils at 237° . It finds a limited use for the preparation of certain medicines (carvacrolphthalein as a purgative, iodinated carvacrol as a substitute for iodoform).



CHAVICOL, *p*-allylphenol, occurs in the oil from betel leaves and in bay oil, and is made synthetically from its methyl ether, estragole. It boils at 273° . When boiled with alkali it isomerizes to anol:

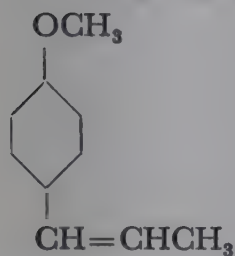


The displacement of the double bond in allylphenols towards the aromatic nucleus under the influence of alkali is a general phenomenon. (Cf. for example, the conversion of eugenol into isoeugenol). Propenyl derivatives are thus formed.

Anol melts at 93° , and is also obtained from anethole by fusion with alkali.



ESTRAGOLE, the methyl ether of chavicol, occurs in many essential oils (e.g. oil of aniseed, star-aniseed oil, bay oil, oil of fennel, tarragon oil). It smells like aniseed. B.p. 215° . The compound is prepared synthetically from *p*-methoxyphenyl-magnesium bromide and allyl bromide:

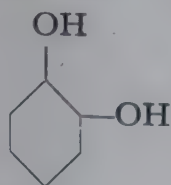


ANETHOLE, *p*-methoxy-propenylbenzene, is one of the chief constituents of oil of aniseed, star-aniseed oil, and oil of fennel. Its sweetish, aniseed smell makes it of use in perfumery and in the manufacture of liqueurs. It melts at $22-23^{\circ}$. It is also often obtained synthetically.

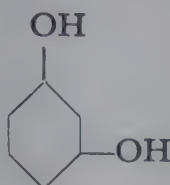
Polyhydric phenols

DIHYDROXYBENZENES

The three theoretically possible dihydroxybenzenes are known as *pyrocatechol*, *resorcinol*, and *hydroquinone*:



Pyrocatechol



Resorcinol



Hydroquinone

1. PYROCATECHOL was first obtained by the dry distillation of species of catechu (Reinsch, 1839), hence its name. It arises from the catechins, tannin-like substances (see p. 566).

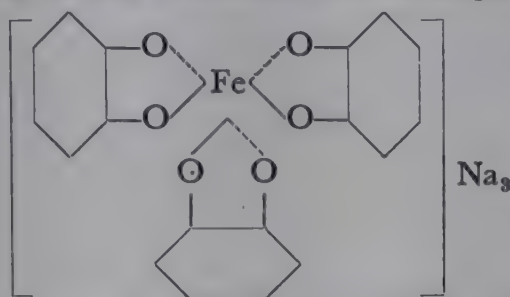
Technically, pyrocatechol is obtained by fusing *o*-chlorophenol with alkalis, or from phenoldisulphonic acid. In the latter case the substance is fused with caustic soda at about 300° , giving a pyrocatecholmonosulphonic acid, from which the sulphonic acid group may be removed by heating with dilute sulphuric acid.

A sulphuric ester of pyrocatechol is a normal constituent of the urine of horses and other animals.

Pyrocatechol crystallizes in white needles, which, however, readily turn brown on exposure to air. It melts at 104° , and boils at 245° . The compound is oxidizable, especially in alkaline solution. It reduces ammoniacal silver nitrate even in the cold, and Fehling's solution on warming. Its use as a photographic developer depends on this reducing power.

The characteristic lead salt of pyrocatechol, $C_6H_4 \begin{array}{c} \diagup O \diagdown \\ \diagdown O \diagup \end{array} Pb$, is practically insoluble and may be used to separate pyrocatechol from resorcinol and hydroquinone.

Ferric chloride gives a green coloration with solutions of pyrocatechol. On the addition of a very small quantity of sodium carbonate or ammonia the green colour becomes red, owing to the formation of a complex iron salt (Weinland):

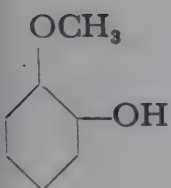


These ferric chloride reactions are very characteristic for *o*-dihydroxybenzene derivatives.

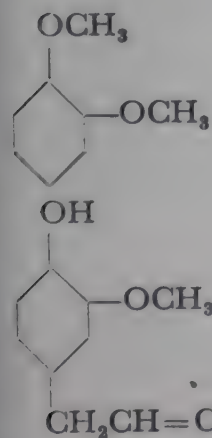
For the oxidation of pyrocatechol to *o*-benzoquinone, see the latter.

DERIVATIVES OF PYROCATECHOL

GUAIACOL (the monomethyl ether of pyrocatechol) was discovered as a distillation product of guaiacum resin (1826, Unverdorben), but is found in larger quantities in beech-wood tar. It can be prepared synthetically by partial methylation of pyrocatechol or from *o*-aminoanisole (*o*-anisidine) through the diazo-compound.



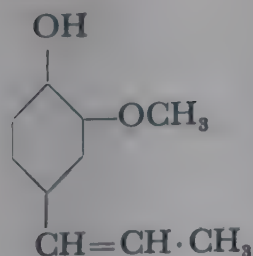
Guaiacol has a strong, characteristic smell. It melts at 28° and boils at 205° . It gives a blue colour with ferric chloride. It is used in medicine in various forms, particularly for the treatment of congestion of the respiratory passages, and tuberculosis. The better known guaiacol preparations are the carbonate, the benzoate (benzosol) and salts of guaiacolsulphonic acids (e.g. sirolin). Vanillin is made commercially from guaiacol.



VERATROLE, the dimethyl ether of pyrocatechol, is often found as a degradation product of naturally occurring substances, e.g. alkaloids. The compound is obtained synthetically by methylation of pyrocatechol or guaiacol. It melts at 22° and boils at 205° .

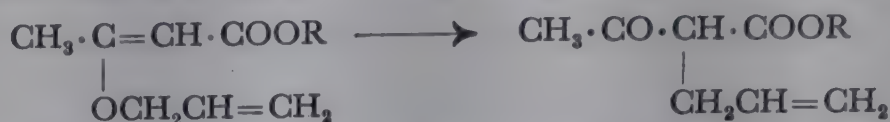
EUGENOL is the odoriferous principle of cloves (*Eugenia caryophyllata*). It boils at 252° . It is used as a starting substance in the preparation of vanillin.

On heating with excess of potassium hydroxide (or using platinized charcoal) eugenol isomerizes to isoeugenol.

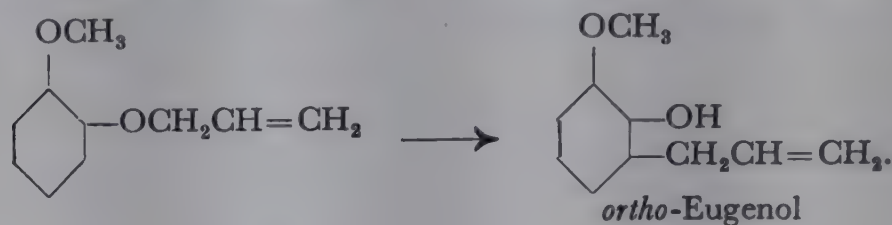


ISOEUGENOL occurs naturally in nutmeg oil and in ylang-ylang oil. It boils at 261° , and melts at 33° . It solidifies in a freezing mixture in the form of needles. On oxidation it gives vanillin.

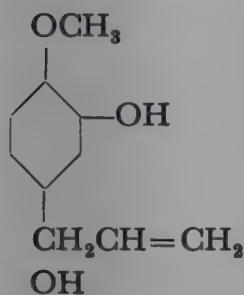
Claisen has discovered a good synthesis of many allyl derivatives of the phenols, which is based on the fact that allyl ethers of enolic compounds and of phenols isomerize to C-allyl compounds on melting. Thus, the allyl ether of acetoacetic ester is easily converted into C-allyl-acetoacetic ester:



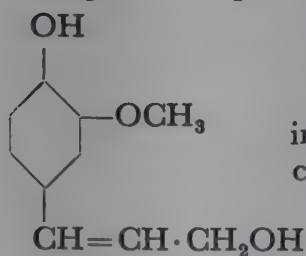
and the allyl ether of guaiacol is converted on melting into *o*-eugenol:



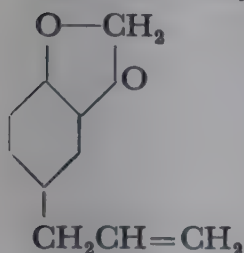
o-Eugenol smells of cloves.



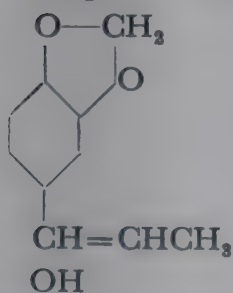
CHAVIBETOL, occurs in betel-nut leaves; m.p. 8.5° , b.p. 254° .



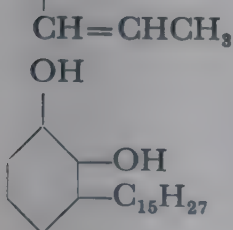
CONIFERYL ALCOHOL is found in the form of the glycoside coniferin in the sap of the cambium of *Coniferae* (Tiemann and Haarmann) and can be converted into vanillin.



SAFROLE occurs in sassafras oil and camphor oil. It is prepared technically from the latter; m.p. 11° , b.p. 233° . Boiling with caustic potash converts it into isosafrole.



ISOSAFROLE. This gives piperonal (see p. 509) on gentle oxidation; b.p. 253° . It occurs naturally in ylang-ylang oil.

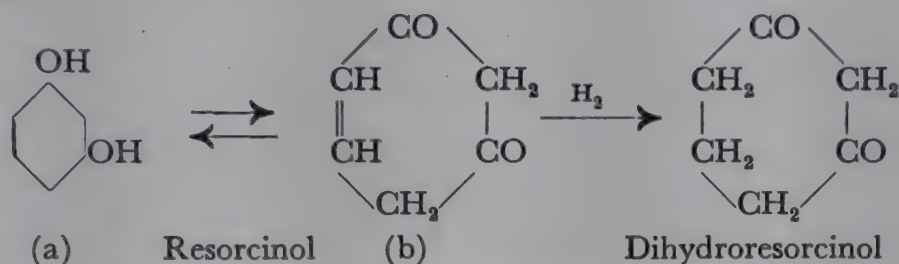


URUSHIOL, from Japan lacquer, the liquid secretion of *Rhus vernicifera*, contains an unbranched, unsaturated side chain in the *ortho*-position to the hydroxyl of pyrocatechol.

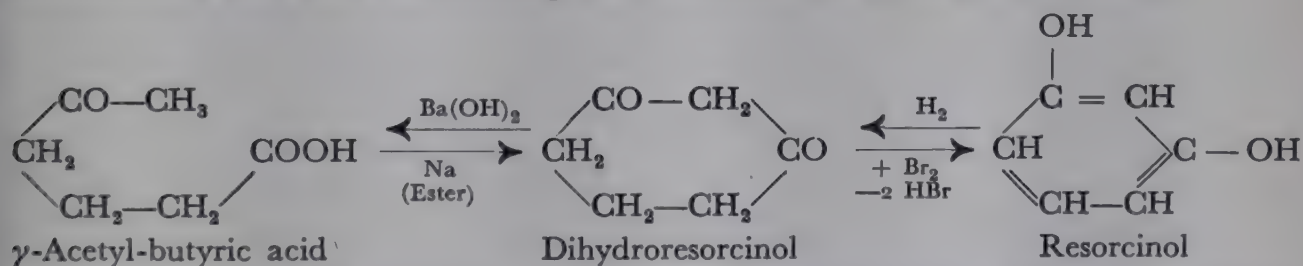
2. RESORCINOL is obtained as a product of degradation of many aromatic compounds on fusion with alkalis, and remarkably enough it is produced not only from *m*-disubstituted products, but also from *o*- and *p*-compounds. Thus, the compound is formed from all three isomeric benzenedisulphonic acids and the three isomeric chlorophenols on fusion with sodium hydroxide. Industrially it is probably always prepared from crude *m*-benzenedisulphonic acid.

Resorcinol crystallizes in colourless prisms and tables; m.p. 110.5°, b.p. 276°. It is readily soluble in water and acts as a reducing agent, particularly in alkaline solution, though less powerfully than pyrocatechol. It deposits silver from ammoniacal silver nitrate only on warming. It gives a violet colour with ferric chloride. Lead acetate gives no precipitate (distinction from pyrocatechol).

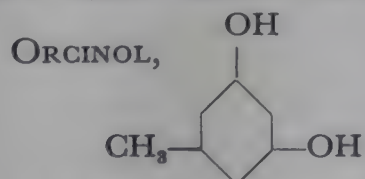
Resorcinol shows a greater tendency than phenol or pyrocatechol to react in the tautomeric carbonyl form (see also phloroglucinol, where this tendency is even more pronounced). To this must be ascribed the fact that resorcinol very easily becomes converted into dihydroresorcinol by taking up two atoms of hydrogen, and this reaction can be brought about even by the action of water and sodium amalgam. The hydrogen adds on across the double bond of the carbonyl form of resorcinol (b):



Since, as Vorländer showed, dihydroresorcinol is easily hydrolysed to γ -acetylbutyric acid by hot baryta water, this reaction, combined with the above, constitutes a method of breaking down resorcinol to an aliphatic compound. Conversely, the ester of γ -acetylbutyric acid condenses with sodium as condensing agent to give dihydroresorcinol, and this can be converted into resorcinol by bromination and then eliminating two molecules of hydrogen bromide:

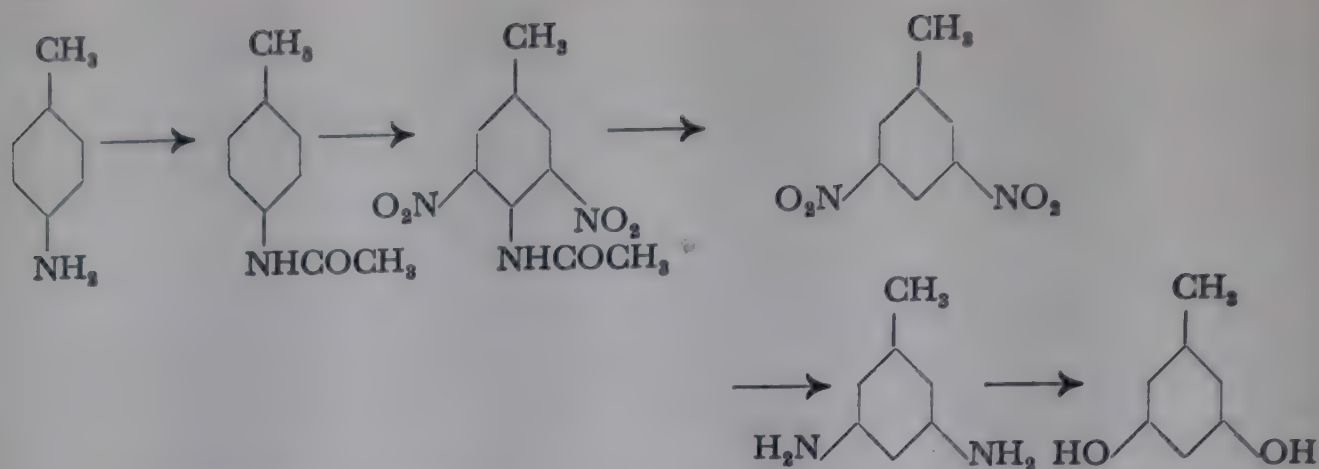


Resorcinol is an important compound in the preparation of numerous dyestuffs, especially those of the azo, fluorescein, and oxazine series (q.v.). Resorcinol and several of its derivatives have a limited use in dermatology on account of their antiseptic or corrosive properties, for the treatment of eczema, etc. 2:4:6-Trinitroresorcinol (*styphnic acid*) is used, like picric acid, as an explosive, as well as for the separation and characterization of organic bases, which frequently form well-crystallized *styphnates*.



a homologue of resorcinol is a constituent of many substances occurring in lichens, from which it may be obtained by suitable methods (Robiquet).

It is obtained synthetically from *p*-toluidine by the following method, which can be readily understood from the scheme below:



Orcinol gives a blue-violet coloration with ferric chloride, and with chloroform and alkali a red coloration is produced which, on dilution with water, becomes yellow showing a green fluorescence. The melting point of anhydrous orcinol is $107-108^{\circ}$.

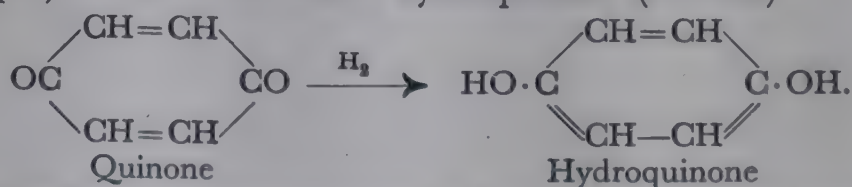
Orcinol is the parent substance of the *orseille* and *litmus* dyes. Orseille, which was already known and often used as a dyestuff in the Middle Ages, is produced from lichens, especially the *Roccella* and *Lecanora* species. The purified lichen is boiled with water, and the extract is treated with ammonia in open vessels. The colouring matter then gradually separates out on standing.

This crude product, orseille, is a mixture of various dyes and other compounds. The colouring matter, called *orcein*, can be isolated from it as a brownish red powder. A similar product is obtained if orcinol solutions are treated with ammonia vapour and air. These dyes, however, are all probably not pure substances. In constitution they perhaps belong to the oxazines (q.v.).

Orseille is only used to-day to a limited extent for dyeing wool and silk. Its violet shades are not at all fast.

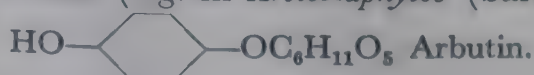
The same lichens which give orseille are also used to obtain litmus. They are treated with ammonia, lime, and potassium carbonate, and the mass is allowed to ferment. Litmus, too, is not a pure substance. By means of alcohol it can be separated into fractions which are soluble and insoluble in alcohol, respectively. Litmus is no longer of importance in the dyeing industry, but it is still occasionally used for colouring foodstuffs. Its most important use is as an indicator for hydrogen and hydroxyl ions, being turned red by the former and blue by the latter.

3. HYDROQUINONE, or QUINOL. Caventou and Pelletier first prepared this compound by distilling quinic acid. It is best made synthetically by the reduction of quinone (q.v.) — hence the name hydroquinone (Nietzki):



On the other hand, the re-oxidation of hydroquinone to quinone readily takes place, even ferric chloride being a sufficiently powerful oxidizing agent to effect the change. *Quinhydrone*, a deeply coloured compound (see p. 579), is produced intermediately. The reducing power of hydroquinone is very great. Silver salts are rapidly reduced by it even at ordinary temperatures. On this fact depends the use of the substance as a photographic developer.

Hydroquinone crystallizes in colourless prisms; m.p. 170° . It occurs in many plants as the glycoside, *arbutin* (e.g. in *Arctostaphylos* (barberry) and in *Ericaceae*).

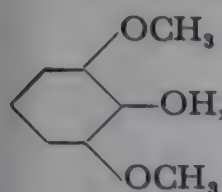


It is usually accompanied by methylarbutin.

TRIHYDROXYBENZENES

1. PYROGALLOL (1:2:3-trihydroxybenzene). This compound was first obtained by Scheele (1786) by heating gallic acid. Technically it is still prepared from gallic acid, by heating with half its weight of water in autoclaves.

Derivatives of pyrogallol are found in nature. The dimethyl ether,

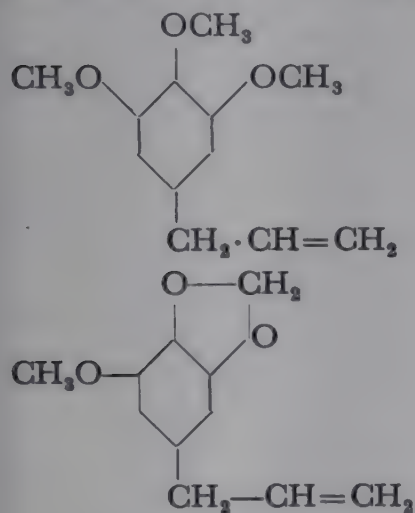


is found in beech-wood tar. Also ellagic acid (see p. 553), hæma-

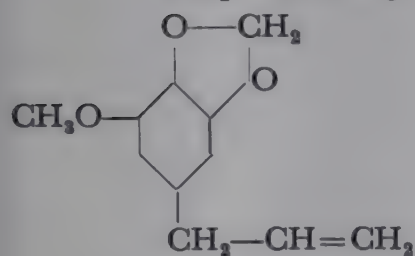
toxylin (see p. 561), some anthocyanins (see p. 562 et seq.) and other substances dealt with below, contain the pyrogallol grouping in their molecules.

Pyrogallol can be sublimed and distilled. It melts at 133° , and boils at 294° . Its outstanding property is the ease with which it is oxidized. Gold and silver salts are reduced instantaneously, and oxygen is so rapidly absorbed by alkaline solutions of pyrogallol that they are used for the absorption and determination of oxygen in gas analysis. Ferrous salts, which contain some ferric salt, give a blue coloration with pyrogallol solutions. The colour changes after a time to brown. Excess of ferric salt oxidizes the pyrogallol to the dye purpurogallin.

Pyrogallol has many technical uses. Its use as a photographic developer is due to its being a reducing agent; this property also governs its use in the treatment of skin diseases (psoriasis, etc.) and as an absorbent for oxygen. In addition it is used in the syntheses of some dyes.

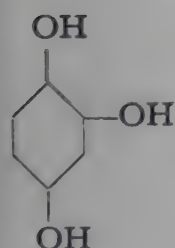


ELEMICIN is the chief constituent of Manila elemi oil. B.p. $144-147^{\circ}$ (10 mm). On boiling with alcoholic potash it isomerizes to the propenyl-compound, *isoelemicin*. B.p. $153-156^{\circ}$ (10 mm).

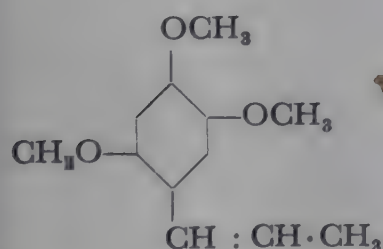


MYRISTICIN is found in oil of mace and oil of parsley. It boils at 149° (15 mm.), and has a powerful smell.

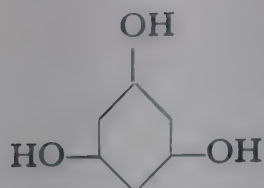
2. HYDROXY-HYDROQUINONE is formed by fusing hydroquinone or *p*-benzenedisulphonic acid with alkali.



Its acetate is readily obtained by the action of acetic anhydride and some concentrated sulphuric acid on quinone. It melts at 140° . It is a strong reducing agent, but has no practical application.

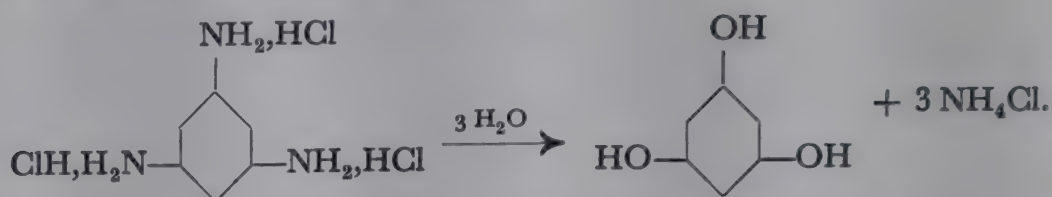


ASARONE. This derivative of hydroxy-hydroquinone is found in essential oils, e.g. in the oil of *Asarum arifolium*, calamus oil, etc. It is odourless. M.p. $62-63^{\circ}$. A geometrically isomeric form (β -asarone) is liquid (b.p. $162^{\circ}/12$ mm).



3. PHLOROGLUCINOL. The symmetrical trihydroxybenzene is a constituent of many naturally occurring substances, e.g. phlorizin (see p. 537), quercitrin (see p. 557), hesperidin (see p. 559), many flavone and anthocyanin pigments (see p. 556 et seq.; p. 562 et seq.), filicic acid (see Ch. 67, section 3), and the catechins (see p. 566).

Phloroglucinol is synthetically best prepared from 1:3:5-triaminobenzene, the hydrochloride of which is boiled with much water. Hydrolytic elimination of the amino-groups takes place:

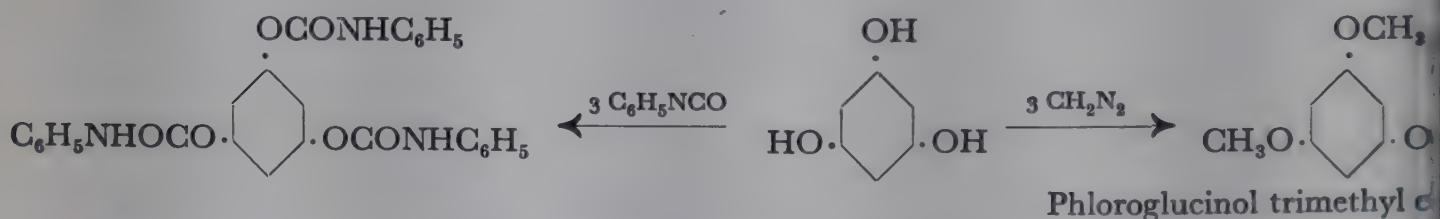


Phloroglucinol is also formed by fusing 1:3:5-benzenetrisulphonic acid with alkali.

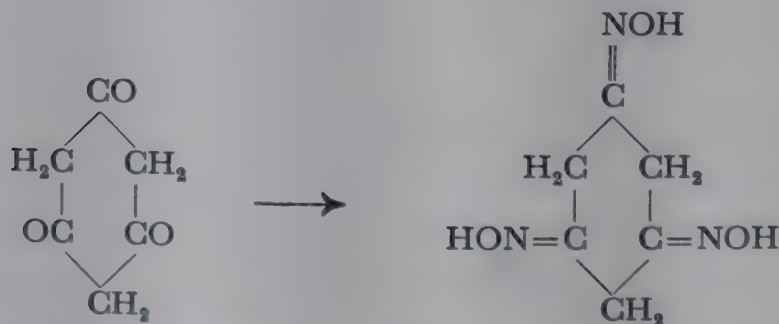
It crystallizes with two molecules of water, and when anhydrous melts at 217–219°. The hydrated compound melts at 113–116°. It tastes sweet. It gives a violet coloration with ferric chloride, and reduces Fehling's solution on heating.

Phloroglucinol often reacts in the tautomeric carbonyl form. The tendency to react as a ketone is even more strongly marked than in the case of resorcinol. However, up to the present it has not been possible to isolate the two tautomeric forms of phloroglucinol in the free state. Only one solid form is known.

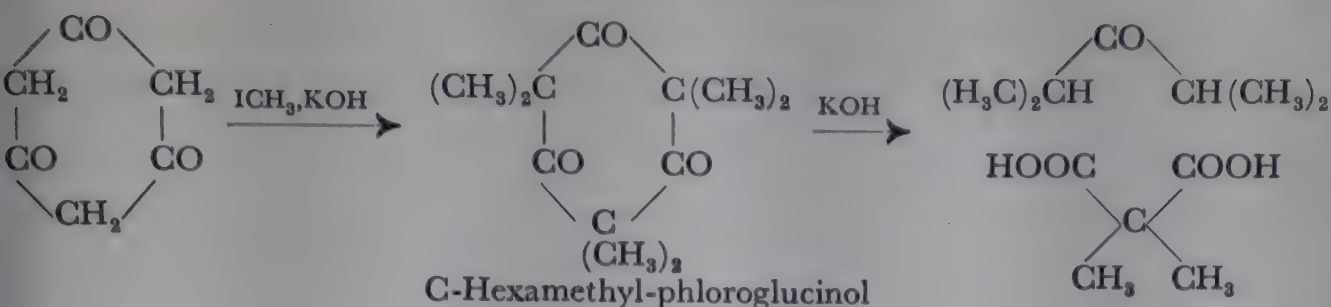
Phloroglucinol reacts as a phenol, for example, with diazomethane and with phenyl isocyanate, forming O-derivatives:



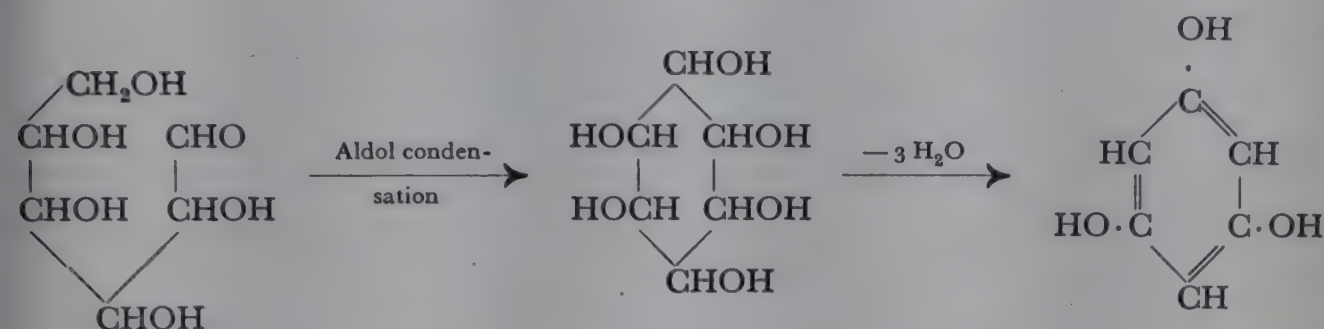
As a ketone it reacts with hydroxylamine, a trioxime being produced:



The alkylation of phloroglucinol with methyl iodide and alkali gives C-alkyl derivatives, and finally C-hexamethyl-phloroglucinol, which, as a β -diketone, readily decomposes into dimethylmalonic acid and tetramethylacetone. This C-alkylation too can best be understood if it is assumed that the phloroglucinol reacts in this case as a reactive methylene compound:



The frequent occurrence of phloroglucinol in plants as well as its relationship to the sugars — from which it differs in containing three molecules of water less — makes it probable that the plant synthesizes the phloroglucinol nucleus from sugars, for instance in the following way:

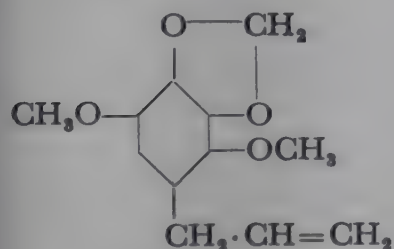
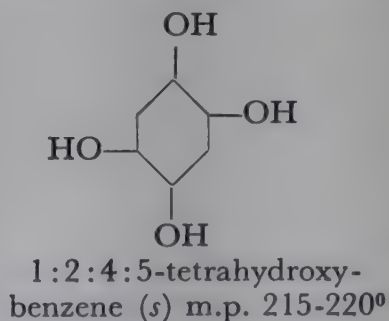
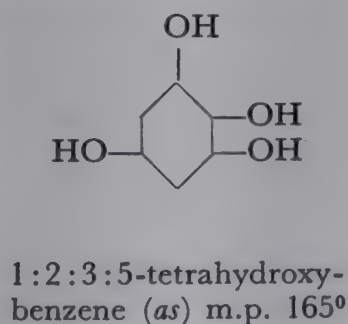
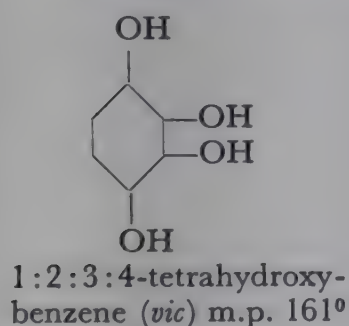


This reaction has not yet been carried out *in vitro*.

Phloroglucinol is used in analytical chemistry for the detection of pentoses (see p. 334) the pentose being boiled with hydrochloric acid, and giving furfural (see Ch. 59) which forms with phloroglucinol an insoluble precipitate. It is also used for the detection of woody substances or lignin (see p. 365) with which it gives a cherry-red colour in the presence of hydrochloric acid.

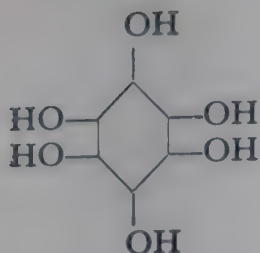
POLYHYDROXYBENZENES

The three possible *tetrahydroxybenzenes* are known, but need not be fully described:

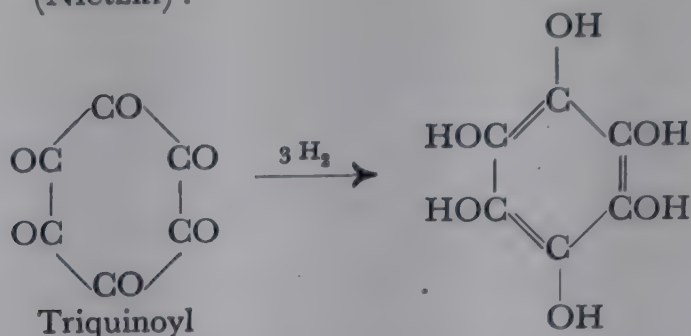


APIOLE (parsley camphor) is derived from vicinal tetrahydroxybenzene. It is found in the plant and fruit of parsley. It has a smell. M.p. 32°, b.p. 294°. On treatment with caustic potash it isomerizes to the propenyl compound, *isoapiole* (with the side chain —CH=CH—CH₃).

PENTAHYDROXYBENZENE. Two substances, obtained in different ways, have been described in the literature as pentahydroxybenzene. They differ, however, in their properties. Further confirmation appears to be necessary.



HEXAHYDROXYBENZENE is obtained from glyoxal (see Ch. 53) or by reduction of triquinoyl (*cyclohexanehexone*) with a solution of stannous chloride in hydrochloric acid (Nietzki):



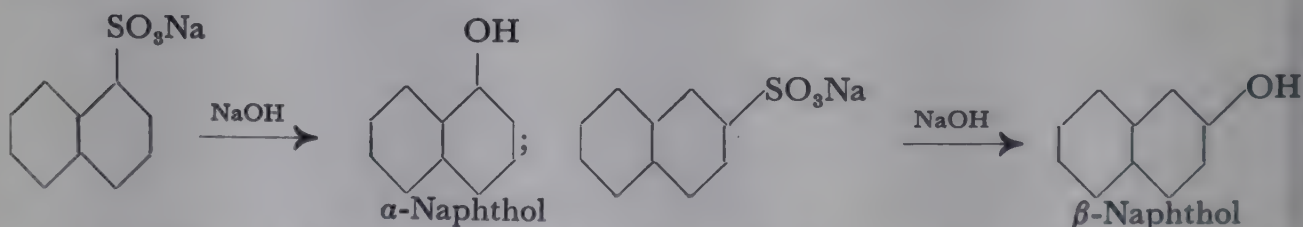
The most convenient method of preparing triquinoyl is the oxidation of 1:2:4:5-tetrahydroxy-3:6-diaminobenzene with nitric acid. The potassium salt of hexahydroxybenzene is potassium carbonyl, $(\text{COK})_6$, which is obtained in the preparation of potassium from potassium carbonate, and also by passing carbon monoxide over heated potassium. On acidification of the potassium carbonyl, hexahydroxybenzene separates.

It forms white needles which are difficultly soluble in cold water, and immediately reduce silver nitrate. At 200° they become grey in colour without melting.

Concerning the reduction of hexahydroxybenzene to inositol, see Ch. 54.

Naphthols

α -Naphthol and β -naphthol are found in small quantities in coal-tar. These substances, which are very important in the manufacture of dyes, are usually manufactured from the corresponding sulphonic acids by fusion with alkali at 300 – 320° .



α -Naphthol is also formed by heating salts of α -naphthylamine with water to 200° .

It is also possible to convert α - and β -naphthylamine into the corresponding naphthols through the diazonium salts.

For the synthesis of α -naphthol from phenylisocrotonic acid, see p. 406.

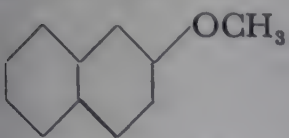
α -Naphthol crystallizes in needles; m.p. 94° , b.p. 279° . β -Naphthol forms shining, rhombic crystals; m.p. 123° , b.p. 285° .

In general character the naphthols completely resemble the phenols of the benzene series. Their hydroxyl group usually reacts more readily than that of the simple phenols, and can be acylated and etherified without difficulty.

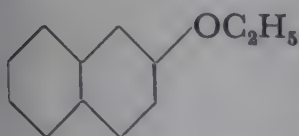
The two naphthols, especially the β -compound are exceedingly important as such, and in the form of their sulphonic acids, nitro- and amino-derivatives, in the synthesis of dyes of all kinds. They will be met with in this connection in

many places in this book. Some acyl derivatives, e.g. the salicylic esters of the two naphthols have a limited use in medicine (as antiseptics).

Of greater importance is the use of β -naphthyl methyl ether and ethyl ether in perfumery.



β -Naphthyl methyl ether, nerolin, smells like orange blossom. M.p. 72° , b.p. 274° . It is prepared by methylation of β -naphthol with dimethyl sulphate.



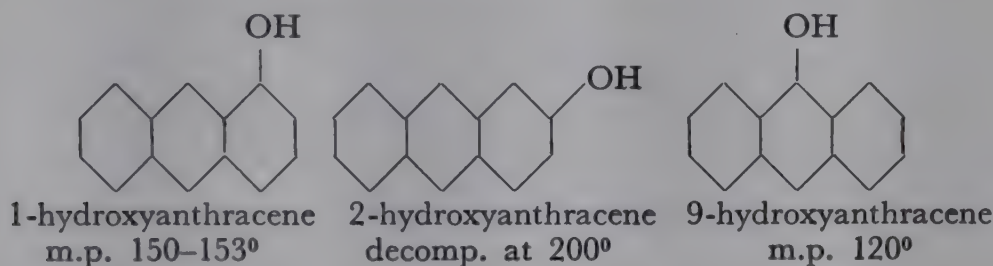
β -Naphthyl ethyl ether, neonerolin, has a fine smell reminiscent of acacia flowers. M.p. 37° , b.p. 275° .

Of the series of theoretically possible dihydroxynaphthalenes, the following have a certain technical importance for the synthesis of dyes:

- 1 : 5-dihydroxynaphthalene, m.p. $258-260^{\circ}$
- 1 : 8-dihydroxynaphthalene, m.p. 140°
- 2 : 3-dihydroxynaphthalene, m.p. 159°
- 2 : 7-dihydroxynaphthalene, m.p. 190° .

Hydroxyanthracenes

Of the three hydroxy-derivatives of anthracene:

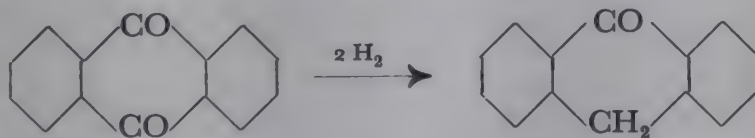


only the last is of any considerable interest.

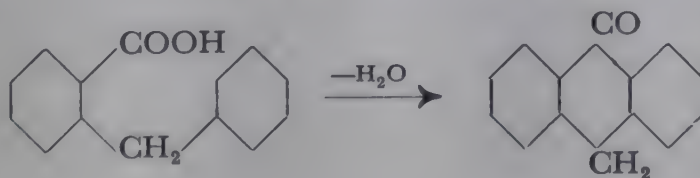
9-HYDROXYANTHRACENE, or ANTHRANOL, is tautomeric with 9-keto-9:10-dihydroanthracene or *anthrone*:



The two tautomers can be isolated under suitable conditions. By the reduction of anthraquinone with tin and acetic acid, or with aluminium and concentrated sulphuric acid



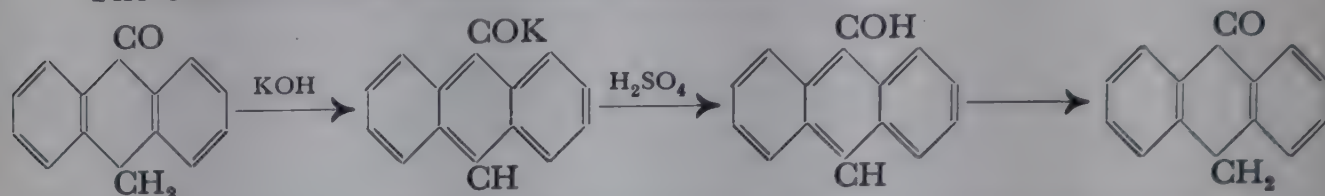
or by heating *o*-benzylbenzoic acid with sulphuric acid (O. Fischer)



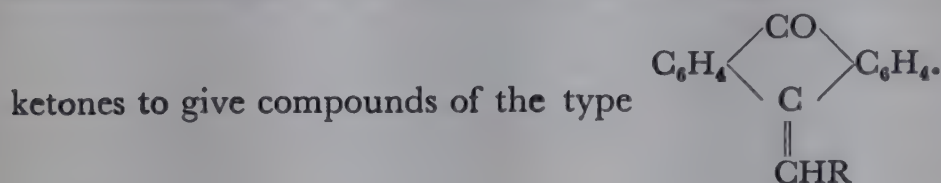
the keto form, *anthrone*, is always obtained (Kurt H. Meyer). It forms colourless needles, melts at 150–155°, and shows, when pure, no fluorescence when dissolved in cold alcohol.

If anthrone is dissolved in alkali and then precipitated from this solution in the cold by the addition of acid, a new compound separates, *anthranol*, which is very readily soluble in alkalis, has a brown colour, and melts at 120°.¹ Its solutions show a strong blue fluorescence. On keeping, even in the solid form, anthranol is very easily converted into anthrone again.

The course of these reactions is as follows:

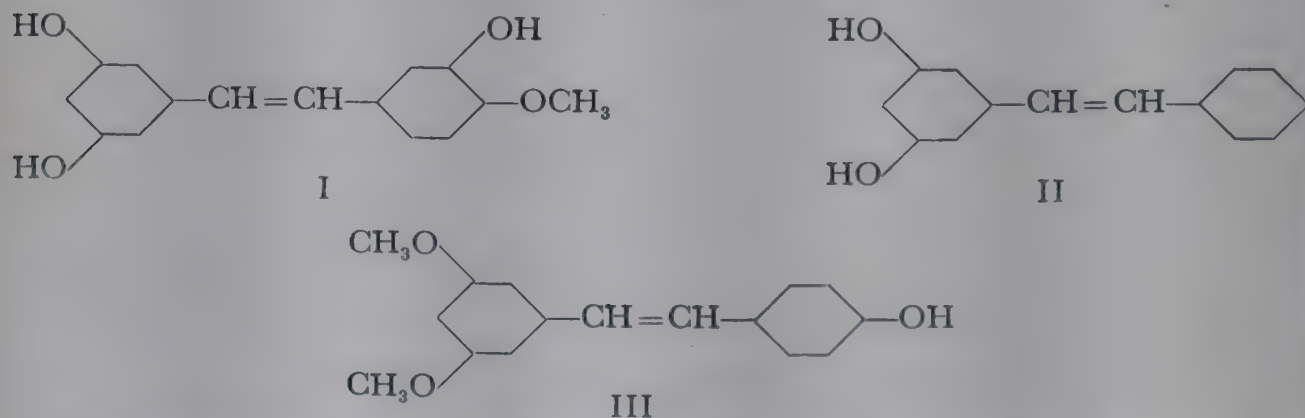


In solution there is always an equilibrium between the two tautomeric forms. The chemical reactions of anthrone are explained by the substance reacting sometimes in the enol (anthranol) form, e.g. in the case of acetylation and salt formation, and sometimes in the keto form (anthrone), e.g. condensation with aldehydes and

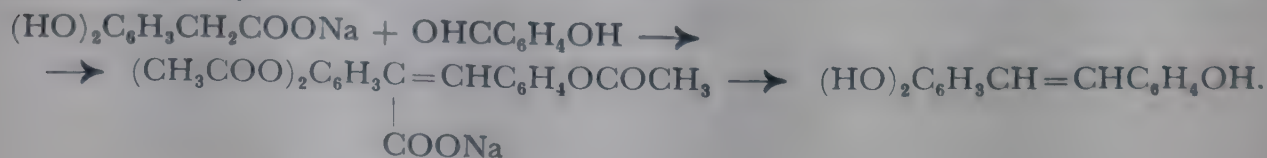


Hydroxy-derivatives of stilbene

From rhubarb roots S. Kawamura isolated a glycoside rhapontin, whose aglycone is 3 : 5 : 3'-trihydroxy-4'-methoxystilbene (I) (rhapontigenin). H. Erdtmann found, in pine wood, 3:5-dihydroxystilbene, *pinosylvic* (II), and its monomethyl ether. He recognized their high toxicity towards fungi and insects, and pointed out that they could be regarded as protective substances for wood. Further, *resveratrol* (3:5:4'-trihydroxystilbene) from white hellebore, *hydroxyresveratrol* (3:5:2':4'-tetrahydroxystilbene), and *pterostilbene* (III), from red sandalwood, belong to this group of compounds:



The constitution of these substances has been verified by syntheses. Resveratrol, for example, is obtained by heating sodium 3 : 5-dihydroxyphenyl acetate with *p*-hydroxybenzaldehyde and acetic anhydride, followed by decarboxylation and hydrolysis of the acetylated acid produced:

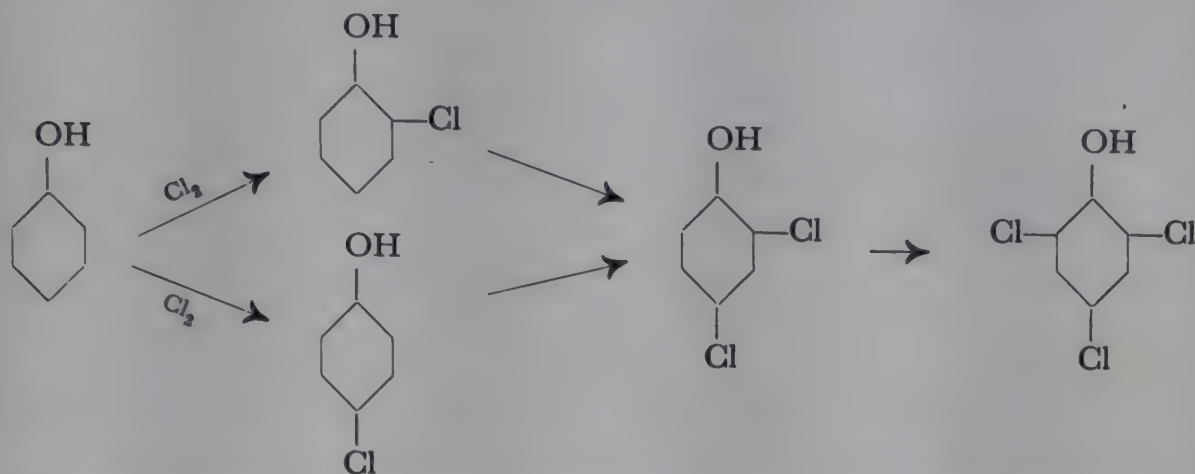


¹ Immersed in a bath at 120°.

CHAPTER 29. HALOGENATED PHENOLS, SULPHONATED PHENOLS, AND NITROPHENOLS

Halogen derivatives of phenols

Phenols are more readily chlorinated and brominated than the aromatic hydrocarbons. The hydroxyl group, being an *ortho-para*-directing substituent, directs the incoming halogen atoms into the *ortho*- and *para*-positions. Thus, phenol itself gives on chlorination *o*- and *p*-chlorophenol, the former predominating. Both compounds give 2:4-dichlorophenol on further chlorination, and finally 2:4:6-trichlorophenol:



The iodination of phenols as a rule also offers no difficulties. In this case it is convenient to work in alkaline solution.

The presence in the nucleus of halogen atoms in the *o*- and *p*-positions with respect to the hydroxyl group, increases the acidity of the phenol. 2:4:6-Tribromophenol even forms a silver salt.

The sometimes rather considerable antiseptic properties of the halogenated phenols, which usually exceed those of the unsubstituted compounds, are noteworthy. Various members of this group are therefore used as disinfectants.

o-CHLOROPHENOL, m.p. 7° , b.p. 175° , has an unpleasant smell.

p-CHLOROPHENOL, m.p. 37° , b.p. 217° , is prepared from phenol and sulphuryl chloride. It is occasionally used as a disinfectant.

2:4:6-TRIBROMOPHENOL, m.p. 96° , is prepared by the action of bromine on phenol. It is used as an antiseptic, and its bismuth salt (xeroform) is used as a bismuth preparation.

p-IODOPHENOL melts at 94° , and 2:4:6-triiodophenol at 156° .

p-CHLORO-*m*-CRESOL, m.p. 66° is prepared from *m*-cresol and sulphuryl chloride. It is a good disinfectant and is often used.

IODINATED CRESOLS have been proposed as substitutes for iodoform.

Phenol- and naphtholsulphonic acids

The sulphonation of phenol gives a mixture of *o*- and *p*-phenolsulphonic acids, which may be separated by means of their barium and magnesium salts. The barium salt of the *o*-acid is more difficultly soluble, and after separating it by crystallization the *p*-acid is separated as the magnesium salt.

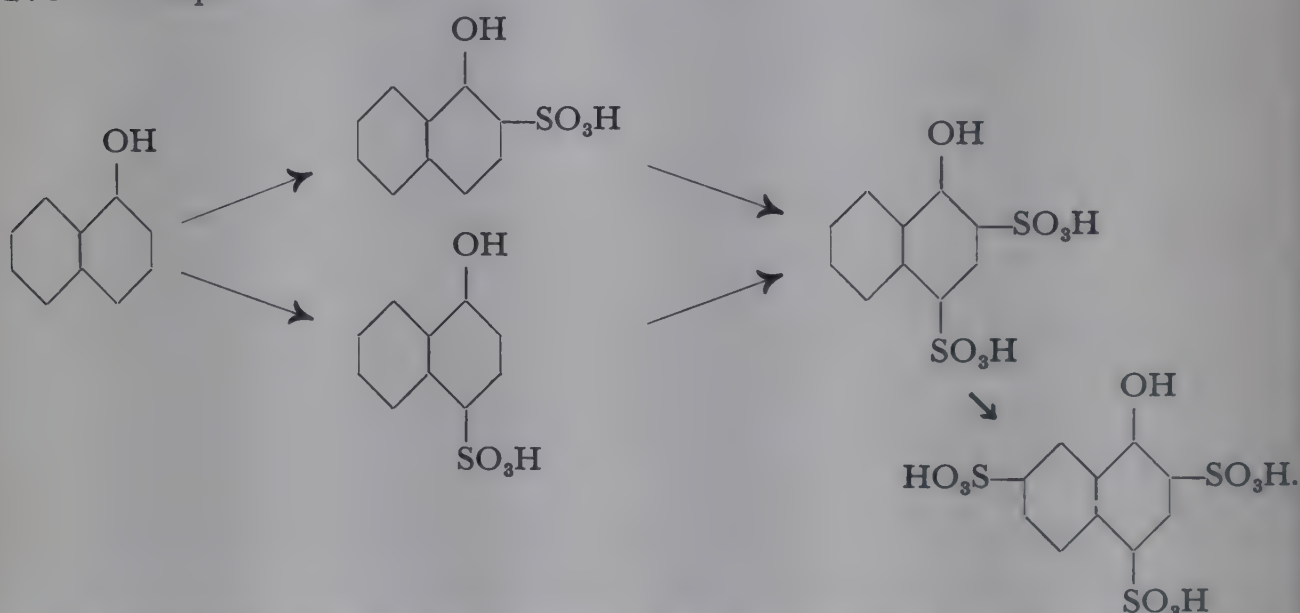
o-PHENOLSULPHONIC ACID is very unstable and gives a violet coloration with ferric chloride.

p-PHENOLSULPHONIC ACID forms deliquescent crystals, and gives a very weak violet coloration with ferric chloride. The compound has been used for the preparation of picric acid, and for the synthesis of various medicinal products, e.g. sozoiodol (sodium salt of 2:6-diiodophenol-4-sulphonic acid), a substitute for iodoform.

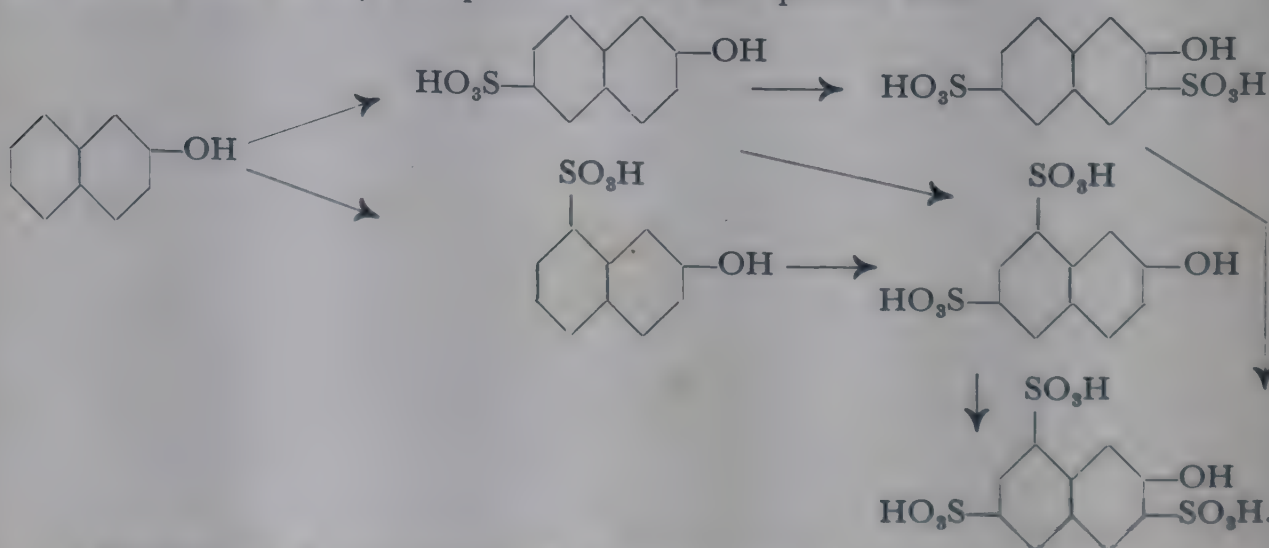
PHENOL-2:4-DISULPHONIC ACID is a substance which forms deliquescent needles, and is the starting material for the preparation of pyrocatechol (see p. 434). The compound is prepared from phenol and fuming sulphuric acid.

Naphtholsulphonic acids.¹ Of much greater importance than the sulphonic acids of the simple phenols are those derived from the naphthols. They are amongst the most important starting products in the dyestuff industry. They are prepared by the action of sulphuric acid on α - or β -naphthol. According to the conditions, various mono- or polysulphonic acids may be obtained.

α -Naphthol is first sulphonated to give 1-naphthol-2-sulphonic acid and 1-naphthol-4-sulphonic acid. By longer action of the sulphuric acid 1-naphthol-2:4-disulphonic acid is formed, and with fuming sulphuric acid 1-naphthol-2:4:7-trisulphonic acid:

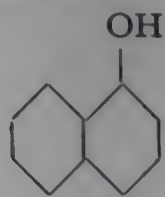


β -Naphthol gives on sulphonation first the unstable 2-naphthol-1-sulphonic acid, and then 2-naphthol-8- and -6-sulphonic acid. By the use of more sulphuric acid 2-naphthol-6:8-disulphonic acid and 2-naphthol-3:6-disulphonic acid are formed, and finally 2-naphthol-3:6:8-trisulphonic acid:

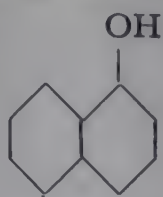


¹ See VAN DER KAM (revised by F. Reverdin and H. Fulda), *Tabellarische Übersicht über Naphthalinderivate*, The Hague, (1927).

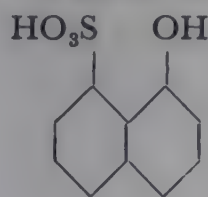
Most of the naphtholsulphonic acids have common names. The most important of these compounds used in the dyestuff industry are given below:



Nevile-Winther's
acid



α -Naphtholsulphonic acid C
(Cleve)



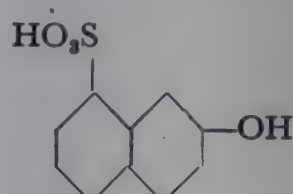
1-Naphthol-8-sulphonic
acid



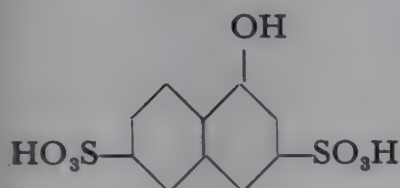
Schaffer's (β -) acid



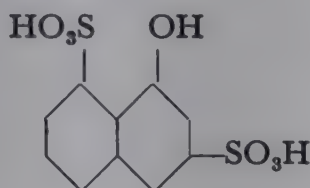
β -Naphtholsulphonic acid
F or δ



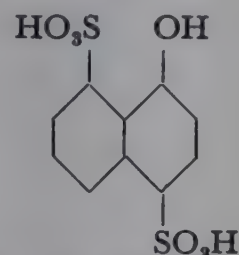
Croceine acid
 β -Naphtholsulphonic acid B.



α -Naphtholdisulphonic
acid RG.
(Gürke and Rudolph)



α -Naphtholdisulphonic acid
 ϵ (Andresen)



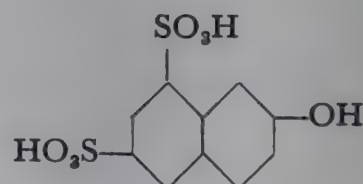
α -Naphtholdisulphonic acid
(Schöllkopf)



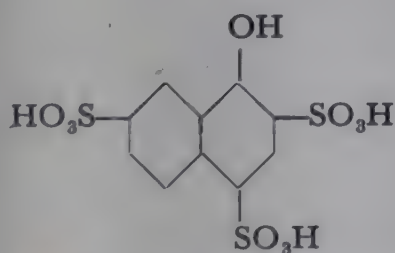
R-acid



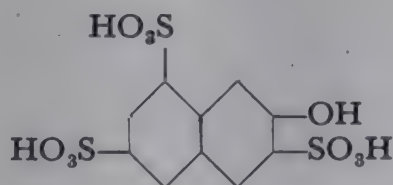
β -Naphtholdisulphonic acid
F or δ



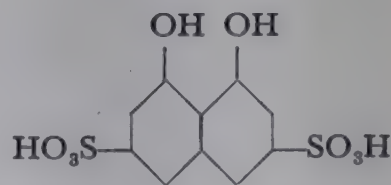
G-acid



1-Naphthol-2:4:7-trisulphonic
acid (for Naphthol Yellow S)



β -Naphthol-3:6:8-
trisulphonic acid



Chromotropic acid

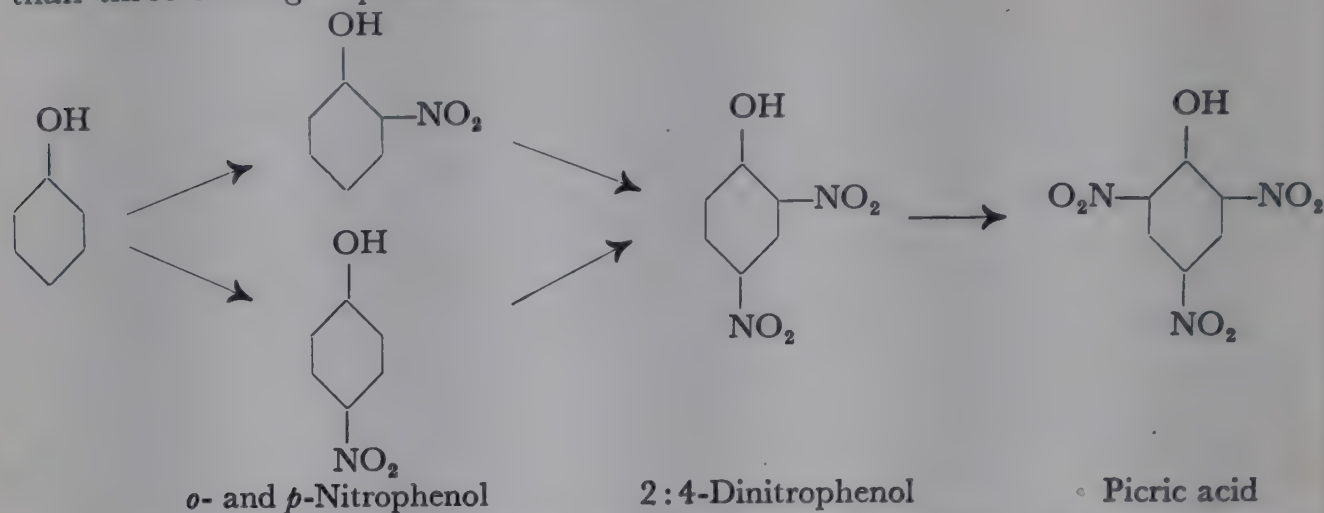
Nitrophenols

Like halogenation, nitration of the benzene nucleus is rendered more easy by the presence of hydroxyl groups. Phenols can frequently be converted into nitrophenols even by dilute nitric acid.

When phenol itself is nitrated, a mixture of *o*- and *p*-nitrophenol is obtained. The two compounds may be separated by distillation in steam, since the *ortho*-

compound only is volatile in steam. *m*-Nitrophenol is prepared from *m*-nitraniline through the diazo-compound.

If more strongly nitrated, *o*- and *p*-nitrophenol give 2:4-dinitrophenol, and finally 2:4:6-trinitrophenol, or picric acid. It is not possible to introduce more than three nitro-groups in this way:



The nitrophenols are stronger acids than the unsubstituted phenols. They decompose carbonates.

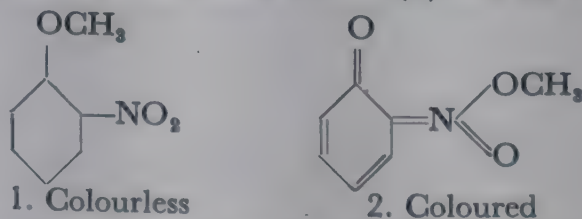
o-NITROPHENOL is yellow, and melts at 45°. It has a powerful odour. It is used for the preparation of *o*-aminophenol, *o*-nitroanisole, and some dyes, e.g. sulphur dyes.

p-NITROPHENOL is colourless, and melts at 114°. It dissolves in alkalis with a yellow colour.

Analogous phenomena are found with many other nitrophenols. The deepening of the colour on conversion of a nitrophenol into its salt is probably connected with structural changes of the molecule, the salt being derived from the "*aci*-form" of the nitrophenol (Hantzsch):



The tautomerism of the nitrophenols is also supported by the fact that in some cases it has been possible to isolate isomeric nitrophenyl alkyl ethers (Hantzsch), one of which is colourless, and the other coloured (red). The constitution (1) is assigned to the first. The coloured ethers (2) are, on the other hand, derived from the *aci*-forms:



The *aci*-nitrophenol ethers are formed by the action of methyl iodide on the silver salts of the nitrophenols. They are usually very unstable and readily isomerize into the normal ethers (1).

p-Nitrophenol is used in the preparation of phenetidine.

m-NITROPHENOL is colourless, and melts at 96°.

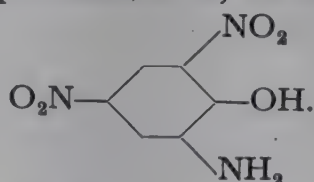
2:4-DINITROPHENOL is yellowish, and melts at 114–115°. It is used in the manufacture of sulphur dyes and 2:4-diaminophenol (a developer). When injected into human beings it produces fever. (It is used in slimming treatments, but is very toxic!)

2:4:6-TRINITROPHENOL, PICRIC ACID, is produced from many organic substances by degradation with nitric acid, since picric acid is the highest nitro-compound of phenol. It was thus discovered by Woulfe (1771) by the action of nitric acid on indigo.

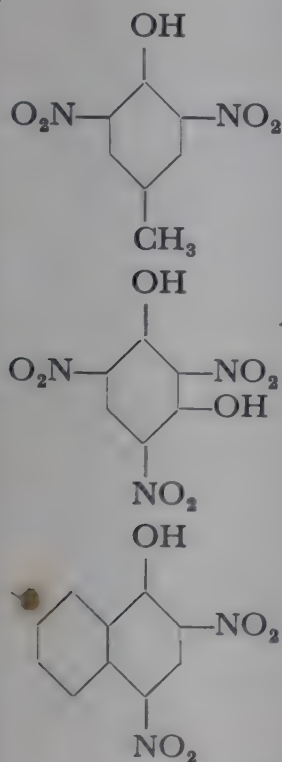
It forms light yellow leaflets or columns, but dissolves in water giving an intensely yellow solution. It is a dye and will colour silk and wool yellow. It melts at 122° .

Picric acid is a strong acid, considerably ionized in aqueous solution. Its dissociation is accompanied by a partial rearrangement of the molecule into the *aci*-form, to which the deepening of colour which occurs when the acid is dissolved in water may also be ascribed. The salts of picric acid crystallize well, and many of them, such as the ammonium and potassium salts, are difficultly soluble in water. They explode when struck, if dry. Also many organic bases form excellent, difficultly soluble picrates, and so picric acid is often used for the isolation and purification of such bases. It can even saturate the residual valencies of some aromatic hydrocarbons (particularly polynuclear hydrocarbons), combining with them to produce difficultly soluble molecular compounds. Thus, for example, naphthalene forms a difficultly soluble picrate, $C_{10}H_8 \cdot C_6H_2(NO_2)_3OH$, by means of which the hydrocarbon can be quantitatively determined.

Picric acid is poisonous. It is no longer used as a dye, but its salts, chiefly its ammonium salt, are used on the large scale for the manufacture of explosives. By partial reduction it gives picramic acid, an intermediate for dyes:

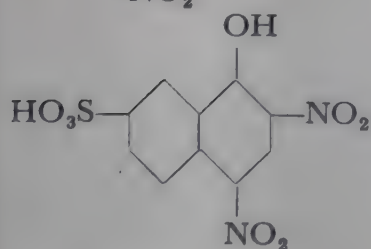


2:6-Dinitro-p-cresol, m.p. 84° , is sometimes used in the form of its sodium salt, known as *Victoria Orange*, for colouring confectionery.



STYPHNIC ACID, m.p. 175° , is obtained by nitrating resorcinol. The compound shows many similarities to picric acid, combining, like the latter, with organic bases giving well-crystallized salts, styphnates, and being used for the separation and purification of these bases. It is also used for the manufacture of explosives.


The ammonium and sodium salts of **2:4-dinitro-1-hydroxy-naphthalene** are used under the name of *Martius' Yellow* for colouring foodstuffs. The compound is prepared by nitrating 2-nitroso- α -naphthol-4-sulphonic acid.



The 7-sulphonic acid of Martius' Yellow is *Naphthol Yellow*, or *Citronine A*, a yellow dye for wool and silk.

CHAPTER 30. AROMATIC ALCOHOLS

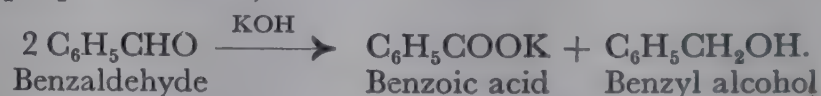
As previously explained, the term "aromatic alcohol" covers those benzene derivatives which contain a hydroxyl group in the side chain. In their chemical properties they resemble in every way the aliphatic alcohols, and not the phenols. They are not soluble in aqueous solutions of alkalis, and are thus much weaker acids than the phenols. Their smell is usually pleasant and aromatic. Their methods of preparation are also analogous to those for aliphatic alcohols. The aromatic alcohols are prepared from the corresponding halogen compounds, or by reduction of aldehydes and esters, and not like the phenols from sulphonic acids or diazonium salts.

BENZYL ALCOHOL, -CH₂OH, the simplest aromatic alcohol, occurs in Peru and Tolu balsams, furthermore in the free form and as an ester (acetate, benzoate, cinnamate) in jasmine, tuberose flower and hyacinth, in flower oils and other essential oils. A glycoside of benzyl alcohol is found in maize.

Benzyl alcohol is prepared by boiling benzyl chloride with potassium carbonate solution, or with water and freshly precipitated lead oxide:



Another method of obtaining the substance, interesting also from the theoretical point of view, depends on the formation of benzyl alcohol and benzoic acid when benzaldehyde is treated with a concentrated solution of potassium hydroxide (disproportionation):



Benzyl alcohol is a liquid, boiling at 206°, and possessing a pleasant smell, which makes it useful in perfumery. In addition, various esters of benzyl alcohol (the acetate, benzoate, cinnamate) which have pleasant smells are used in perfumery. In recent times benzyl alcohol and its esters have been used as local anæsthetics, though they are not very powerful.

PHENYLETHYL ALCOHOL, C₆H₅CH₂CH₂OH. This substance plays an important part in the perfumery industry owing to its very pleasant odour. It occurs in rose oil and neroli oil and is usually made on the technical scale by the reduction of phenylacetic ester with alcohol and sodium (Bouveault and Blanc):



Another process depends on the reaction between phenylmagnesium chloride and ethylene oxide:

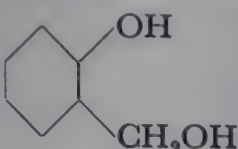


It boils at 220–222°.

PHENYLPROPYL ALCOHOL (hydrocinnamyl alcohol), C₆H₅CH₂CH₂CH₂OH, is found as the cinnamic ester in various balsams and resins. It is made artificially by the reduction of cinnamic alcohol with sodium amalgam, or from ethyl cinnamate by the method of Bouveault and Blanc. It boils at 235°. It has a hyacinth-like odour, and is used in the form of its esters in blending perfumes.

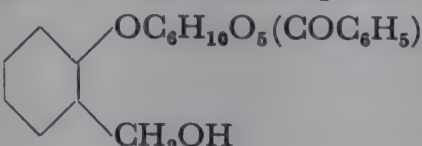
CINNAMIC ALCOHOL, $C_6H_5CH=CH \cdot CH_2OH$ (styrone), is found as cinnamyl cinnamate (styracine) as the chief constituent of storax and also occurs in other balsams and resins. It is obtained technically by the hydrolysis of storax, or from cinnamic aldehyde (q.v.) by reduction.

Cinnamic alcohol crystallizes in white needles, melting at 33° and boiling at 257° . It smells like hyacinths and is used in perfumery.

SALIGENIN, , is at one and the same time a phenol and an

aromatic alcohol. Its glycoside, *salicin*, $C_6H_4(OC_6H_{11}O_5)(CH_2OH)$ (m.p. 201°), occurs in the leaves and bark of *Salix helix* and other species of willow; acids and enzymes convert it into glucose and saligenin.

In the bark and leaves of various species of poplar the 6-benzoyl derivative

of salicin, POPULIN,  is found.

Saligenin is a solid, melting at 82° . Since it is a phenol it dissolves in alkalis and gives a blue colour with ferric chloride.

For the phenolic alcohol, *coniferyl alcohol*, see p. 436.

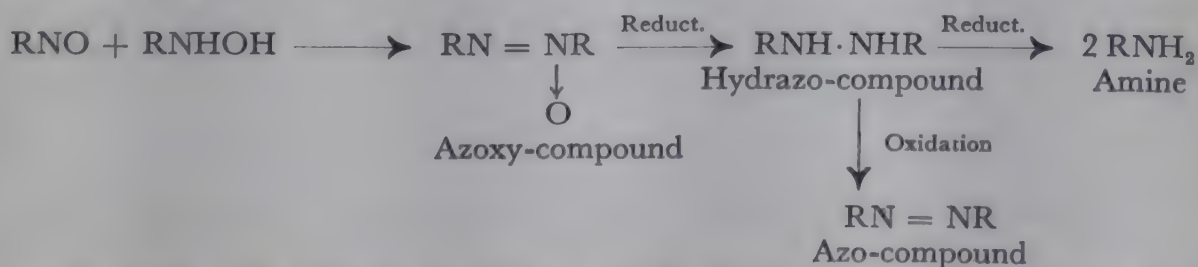
CHAPTER 31. AROMATIC AMINES

METHODS OF PREPARATION. 1. The most important method of preparation of the aromatic amines is the reduction of nitro-compounds. In the aliphatic series, where the nitro-compounds are relatively difficult to obtain, this method is only of secondary importance.

The reduction of a nitro-compound to an amine occurs through various intermediate stages. In *acid* solution a nitroso-compound is first formed, followed by a hydroxylamine derivative, and finally the amine:



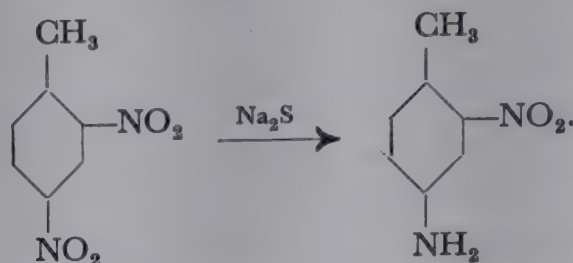
In *alkaline* solution the reduction takes the same course initially; nitroso- and hydroxylamine derivatives are produced. These, however, then condense to form azoxy-compounds, because their combination takes place more rapidly than their further reduction. Azoxy-compounds give hydrazo-compounds by further reduction, and these are oxidized by atmospheric oxidation to azo-compounds, or, on the other hand, by the action of a further quantity of the reducing agent, are reduced to amines:



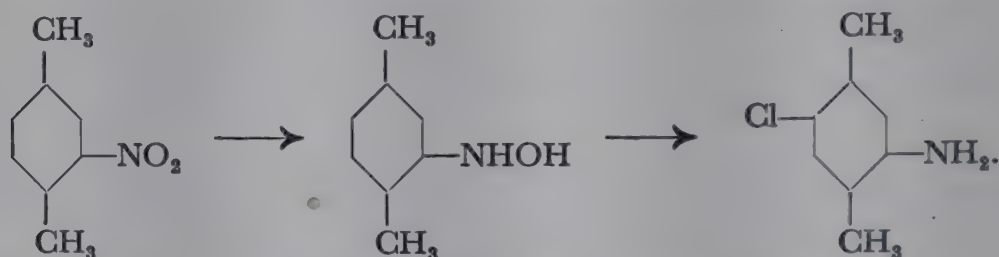
The choice, and method of use of the reducing agent depends upon which stage of the reduction it is desired to reach.

(a) With hydrogen sulphide and alkali-metal sulphides, aromatic nitro-compounds are reduced in the cold (0°) to the hydroxylamine stage. On heating, the reaction goes further to the amine stage.

The alkali-metal sulphides are particularly useful for the reduction of poly-nitro-compounds, since it is often possible, by their aid, to carry out partial reductions, and to convert only one of a number of nitro-groups into the amino-group. As a rule the nitro-group in the *p*-position to a substituent is the most readily reduced:



(b) Nascent hydrogen, produced from a metal and an acid, is a frequently used reducing agent for the preparation of amines from nitro-compounds. Usually tin, iron, or zinc, and hydrochloric acid are used. Stannous chloride and hydrochloric acid are also employed. If the reaction is carried out in concentrated hydrochloric acid solution, however, chlorinated by-products are occasionally formed, which are probably produced from the hydroxylamine stage:



The chlorination can be prevented by the addition of a ferrous salt.

(c) Sodium hydrosulphite, $\text{Na}_2\text{S}_2\text{O}_4$, readily reduces nitro-compounds even in the cold. In addition to the amines, sulphamic acids are occasionally formed as by-products.

(d) The electrolytic reduction of nitro-compounds to amines is also often used. If the process is carried out in concentrated sulphuric acid solution *p*-aminophenol is obtained instead of aniline from nitrobenzene. The reason for this lies in the fact that phenylhydroxylamine, the intermediate product in the reduction, rearranges to *p*-aminophenol in the presence of the concentrated acid, as mentioned above (p. 423):



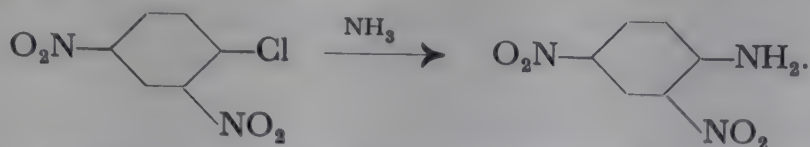
(e) Titanium trichloride reduces nitro-compounds smoothly to amines. The violet colour of the titanium chloride disappears, and the method can thus be used for the volumetric estimation of nitro-groups:



(f) Finally it must be mentioned that catalytically activated hydrogen is also a suitable reducing agent.

2. Aromatic halogen compounds are not as a rule easily converted into amines. Those halogenated benzene derivatives in which the halogen is activated

by nitro-groups in the *o*- or *p*-positions, are exceptions. They react with ammonia and amines even at moderate temperatures:



The simple aromatic halogen compounds, such as chlorobenzene, must be heated to very high temperatures with ammonia in autoclaves, to convert them into amines. The presence of copper, which acts as a catalyst, is advantageous. Under these conditions it is possible to convert chlorobenzene to the extent of 80 per cent into aniline. The halogen can also be fairly readily replaced by the amino-group by the action of potassamide on phenyl halides in liquid ammonia.

3. A third method of preparation of amines consists in heating phenols with the double compound of zinc chloride and ammonia to about 300° (see p. 430). It has been pointed out there that the conversion of polyhydric phenols and naphthols into amines proceeds more readily.

4. Aromatic carboxylic acids can be converted into amines in the same way as aliphatic acids, through the amides (Hofmann degradation) or the azides (Curtius degradation). The reactions are exactly analogous to those in the aliphatic series (see p. 130).

Properties of the aromatic amines. The simplest aromatic amines are liquids, the higher ones are solids. They are usually difficultly soluble in water, but the solubility is greater the more amino-groups are present. The diamines are fairly readily soluble, and the triamines even more soluble. Liquid amines have a weak aromatic smell.

The basicity of the aromatic amines is considerably weaker than that of the aliphatic amines. The benzene nucleus which increases the acidity of the hydroxyl group so that phenols are stronger acids than the alcohols, correspondingly reduces the basic character of the amino-group. The arylamines react neutral towards litmus, but they form stable salts with mineral acids, which, however, dissolve in water giving an acid reaction, owing to partial hydrolysis. It is owing to the production of such salts that the amines, in spite of their weak basic character, precipitate metallic hydroxides from solutions of metallic salts, since they fix the acid produced by the hydrolysis of the metal salt, thus causing progressive new formation of the hydroxide.

The basic character of the amino-groups is even further reduced when there is more than one phenyl radical attached to the amino-group. Diphenylamine, $\text{C}_6\text{H}_5\text{NHC}_6\text{H}_5$, still furnishes salts with strong acids, but they are completely hydrolysed in aqueous solution. In triphenylamine, $(\text{C}_6\text{H}_5)_3\text{N}$, the basicity is even less marked.

In their chemical properties, the aromatic amines resemble, in general, their aliphatic analogues (q.v.). They can be alkylated in the normal way, producing compounds up to quaternary ammonium salts:



The quaternary ammonium bases react, as in the aliphatic series, strongly alkaline.

By the introduction of acid radicals into the amino-groups, aromatic amines

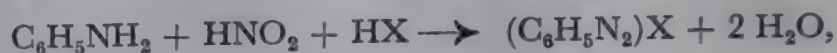
form derivatives of amides, which are called "*anilides*": $\text{Aryl-NH}\cdot\text{COR}$. They are neutral. See further p. 469 ff.

Primary aromatic amines give the carbylamine reaction, like the corresponding aliphatic compounds, when warmed with chloroform and alkali:



Other reactions proceed somewhat differently according as an aliphatic or an aromatic amine takes part. To these belong:

(a) The action of nitrous acid on primary amines. In the case of the aliphatic amines this leads to alcohols. Aromatic primary amines, however, in mineral acid solution react with nitrous acid forming diazonium salts (see p. 472):



which, only on long standing, or on warming the solution, decompose with evolution of nitrogen, giving hydroxy-compounds, the phenols:



On closer investigation the difference in the behaviour of aromatic and aliphatic primary amines towards nitrous acid is not a fundamental one. In the aliphatic series, diazonium salts occur as the first reaction products. They are, however, also so unstable, that under ordinary conditions they cannot be detected, and only their decomposition products, alcohols, are found.

(b) With carbon disulphide the primary amines of the aliphatic series (see p. 132) form dithiocarbamic acids, $\text{C}_n\text{H}_{2n+1}\text{NHCSSH}$. In the case of aromatic amines two molecules of the amine combine with one molecule of carbon disulphide forming derivatives of thiourea:



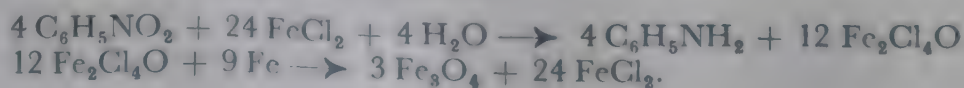
Aromatic monoamines

Aniline. This, the simplest and most important amine of the aromatic series, was discovered independently by various observers. In 1826 Unverdorben obtained it by distillation of indigo with lime; he called it "crystalline". In 1834 Runge detected it in coal-tar by the bleaching powder reaction, and gave the compound the name "cyanol". In 1841 Fritzsche obtained it by heating indigo with caustic potash; he called it "aniline" (from the Spanish, *añil*, meaning *indigo*). In the same year Zinin obtained it by reduction of nitrobenzene and called it "benzidam". The identity of all these substances was recognized by A. W. Hofmann (1843).

Aniline is found in coal-tar, but in very small quantities. Technically it is always prepared from nitrobenzene, which is reduced with iron and dilute hydrochloric acid. The amount of hydrochloric acid necessary is only about 1/40 of that required by the equation



as the ferrous chloride produced is utilized for the further reduction, probably as indicated (schematically) by the equations:



The direct synthesis of aniline from benzene and ammonia in the presence of oxygen in an electric field of high frequency and high voltage is of theoretical interest. The reaction, which will give up to 15 per cent of aniline, proceeds according to the equation:



Aniline is a colourless oil, difficultly soluble in water, with a weak aromatic smell. It boils at 182° , and melts at 6° . In the air it soon becomes brown. Breathed in large quantities, aniline vapour may produce symptoms of poisoning (giddiness, excitedness).

A number of colour reactions are suitable for the detection of aniline. An aqueous solution of aniline gives a violet colour with a solution of bleaching powder, and with potassium dichromate and sulphuric acid a red colour is first produced, which then changes to blue.

Aniline is a most important starting material for the preparation of dyes and intermediates (azo-dyes, Aniline black, Aniline blue, fuchsin, etc.).

For many purposes it is necessary to have the purest possible aniline, free from homologues, which is prepared from pure benzene, through nitrobenzene. This is known in commerce as "blue aniline". Moreover, a "red aniline" is made, for the preparation of the red magenta dyes, which is composed of aniline (about 33 per cent), *p*-toluidine (about 23 per cent) and *o*-toluidine (about 44 per cent).

ALKYLATED ANILINES. If aniline is boiled with methyl iodide, by the method of A. W. Hofmann, a mixture of mono- and dimethylaniline with the quaternary ammonium salt is produced.

If an aniline salt, best the sulphate, is heated with methyl alcohol in an autoclave, only the mono- and dialkyl compounds are chiefly obtained. According to the quantity of methyl alcohol used, and the temperature at which the reaction is carried out, either the mono- or dialkyl compound is produced in excess:

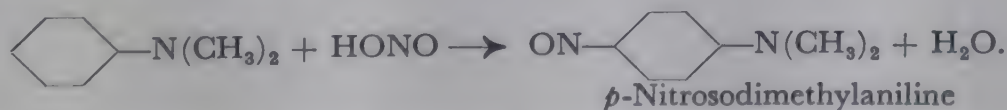


The separation of the two substances cannot be effected by fractional distillation as their boiling points are almost the same. It is, however, possible to separate them by treating them with acetic anhydride, or toluenesulphonyl chloride, as only the secondary base, monomethylaniline, is capable of forming an acetyl or toluenesulphonyl derivative, dimethylaniline not reacting.

MONOMETHYLANILINE boils at 196° . On heating to 330° it rearranges partially by the wandering of the methyl group, to *p*-toluidine:



DIMETHYLANILINE; b.p. 194° , m.p. 2.5° . The *para*-position to the dimethylamino-group is reactive in dimethylaniline and other dialkylanilines. It readily reacts with different reagents. Thus, nitrous acid gives the green *p*-nitrosodimethylaniline with dimethylaniline:

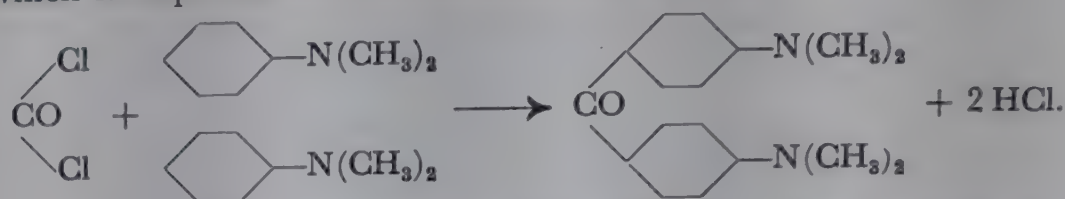


Since, as mentioned above, primary aromatic amines react with nitrous acid to form diazonium salts, and the secondary amines, as in the aliphatic series, give nitrosamines:



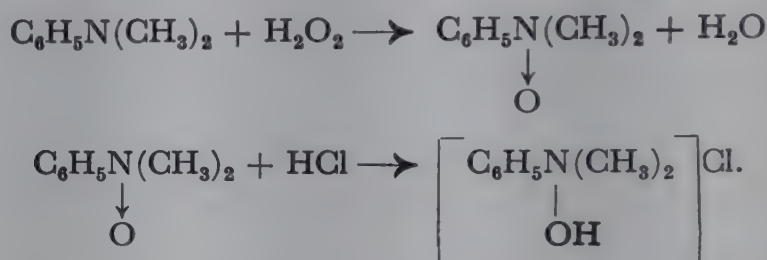
nitrous acid can be used to distinguish between the three types of amine.

Dimethylaniline also reacts easily with various acid chlorides, e.g. phosgene, the *p*-position being attacked. The reaction product is a ketone, known as *Michler's ketone*, which is important in the manufacture of dyes:



Other condensations of the dialkylanilines, e.g. with aldehydes, will be dealt with in later chapters (see, for example, the synthesis of Malachite green).

It may also be mentioned that dimethylaniline possesses the characteristic property of tertiary amines of forming an amine oxide, dimethylaniline oxide (m.p. 153°), by the action of hydrogen peroxide. This is a base and combines with hydrogen chloride to give a substance of the ammonium salt type:



PHENYLATED ANILINES. DIPHENYLAMINE is obtained by heating equimolecular amounts of aniline and aniline hydrochloride in autoclaves to $200\text{--}230^\circ$:



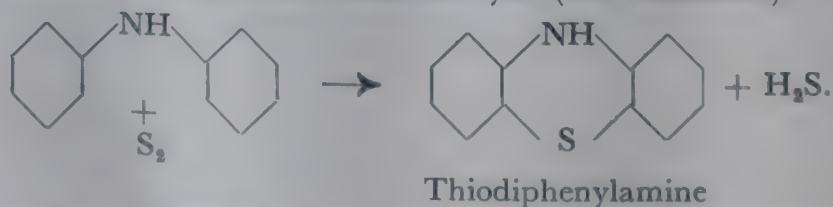
It forms white, lustrous leaflets, m.p. 54° , b.p. 302° . It is insoluble in water and dilute hydrochloric acid. It forms salts with concentrated mineral acids, which, however, are hydrolysed even by water. The basic character of the compound is therefore very weak.

Diphenylamine is used as a reagent for nitric acid, which colours a solution of diphenylamine in concentrated sulphuric acid deep blue. The cause of the colour reaction is the formation of imonium salts of diphenylbenzidine (Kehrmann):



Diphenylamine is also used as a stabilizer for nitrocellulose, and for the production of some dyes.

When melted with sulphur, diphenylamine gives thiodiphenylamine, the parent substance of an important class of dyes (the thiazines):



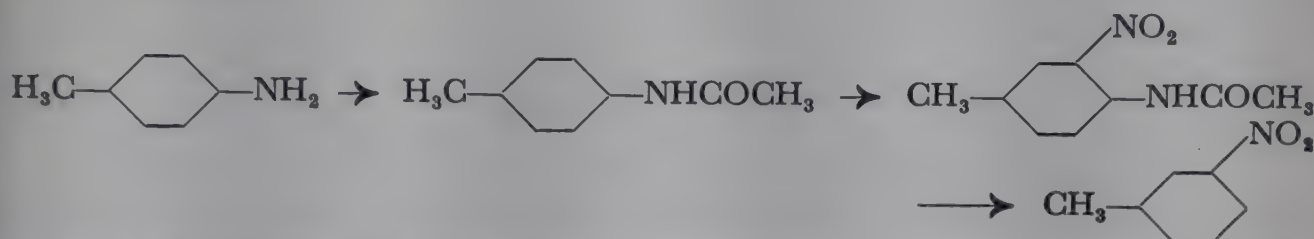
TRIPHENYLAMINE, $(\text{C}_6\text{H}_5)_3\text{N}$, is formed by heating the potassium compound of diphenylamine with bromobenzene in a sealed tube:



or, more conveniently, by boiling together for some time diphenylamine, iodo-benzene, potassium carbonate, and copper powder.

Triphenylamine is a solid melting at 127°. Its basic character is so weak that it does not form salts with either sulphuric or hydrochloric acid. A perchlorate and a fluoride are, however, known. When treated with a solution of sodium nitrite and concentrated sulphuric acid, or when heated with oxalic acid, triphenylamine gives blue dyes.

Homologues of aniline. THE TOLUIDINES. The three isomeric toluidines are always obtained from the corresponding nitrotoluenes by reduction, the reaction being carried out industrially in a similar way to the preparation of aniline from nitrobenzene. For the synthesis of *o*- and *p*-nitrotoluene by nitration of toluene, see Chapter 25. *m*-Nitrotoluene is most conveniently obtained in the pure form from *p*-toluidine:



All three toluidines have very similar properties, and show a close relationship with aniline:

	b.p.	m.p.	m.p. of the acetyl derivative
<i>o</i> -Toluidine	200°	—16.4°	110°
<i>m</i> -Toluidine	203°	—31.2°	65°
<i>p</i> -Toluidine	200°	43°	150°

The toluidines can be separated by making use of the different solubilities of their acetyl derivatives. A mixture of *o*- and *p*-toluidine can be separated by using the fact that *o*-toluidine oxalate is readily soluble in ether, whilst *p*-toluidine oxalate is almost insoluble in ether.

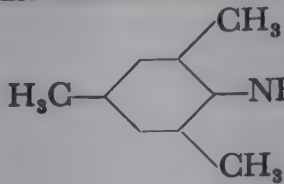

The toluidines are extensively used in industry for the synthesis of dyes (azo-dyes, primuline and fuchsin dyes etc.).

XYLIDINES. If, as happens on the technical scale, the mixture of nitroxylenes obtained by nitration of crude xylene, is reduced, a mixture of five isomeric xylidines is produced:

<i>p</i> -Xylidine	" <i>m</i> -Xylidine" 4-Amino-1:3-dimethylbenzene	2-Amino-1:3-dimethylbenzene	3-Amino-1:2-dimethylbenzene	4-Amino-1:2-dimethylbenzene
b.p. 215°	b.p. 212°	b.p. 216°	b.p. 239°	b.p. 226°

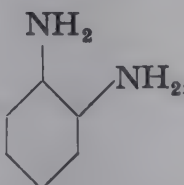
The chief constituent of the mixture is *m*-xylidine (40–60 %); *p*-xylidine occurs to the extent of 10–20 %. These two compounds are also the most important technically. They are used for the manufacture of dyes (especially azo-dyes).

There are various methods for separating them from the crude mixture of bases. If, for example, hydrochloric acid is added to crude xylidine, a mixture of the hydrochlorides of *m*- and *p*-xylidine crystallizes out, whilst the other bases remain as hydrochlorides in the solution. *m*- and *p*-Xylidine are separated through their sulphonic acids (*m*-xylidinesulphonic acid is difficultly soluble in water, whereas the *p*-compound is more readily soluble), or in other ways.

AMINES OF HIGHER BENZENE HOMOLOGUES are known in the form of many representatives (e.g. *mesidine*, , a derivative of mesitylene; *cumidine*, , a derivative of cumene, etc.). They do not merit further description.

Aromatic diamines

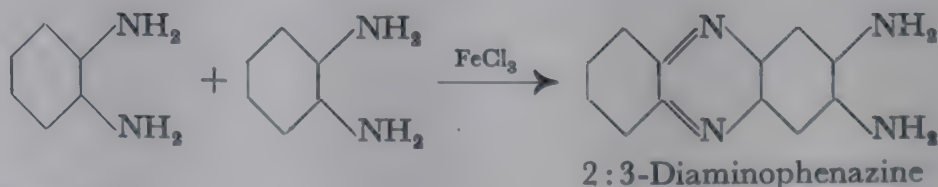
Three isomeric diamines, known as *phenylenediamines*, are derived from benzene. ("Phenylene" is a radical derived from benzene by loss of two hydrogen atoms). All three phenylenediamines are solids which crystallize well, and which dissolve fairly easily in cold water, and quite readily in hot water. In common with the polyhydric phenols they are readily oxidized. They cannot therefore be kept indefinitely in the air, but soon become coloured and decompose. Their salts are more stable.

ORTHO-PHENYLENEDIAMINE, , This compound is prepared by the

reduction of *o*-nitraniline, preferably with zinc dust and alkali. M.p. 102°, b.p. 256–258°.

The compound shows a characteristic tendency to ring closure, owing to the favoured positions of the two amino-groups for ring formation.

It is oxidized by ferric chloride in acetic acid solution to 2:3-diaminophenazine:



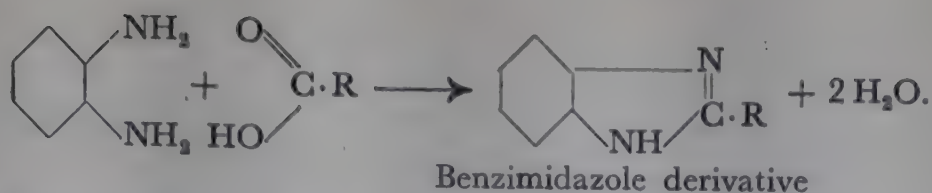
Further reactions are:

(a) *o*-Phenylenediamine and nitrous acid give azoimidobenzene:

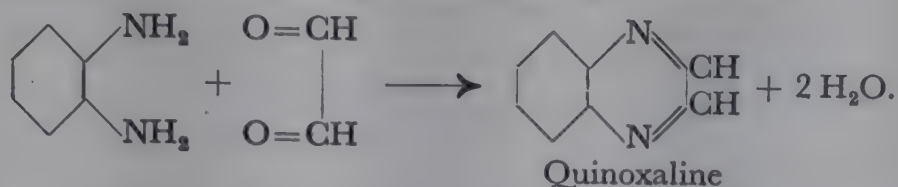


(Cf. the behaviour of the *m*- and *p*-diamines towards this reagent).

(b) *o*-Phenylenediamine and anhydrous carboxylic acids give substituted benzimidazoles:



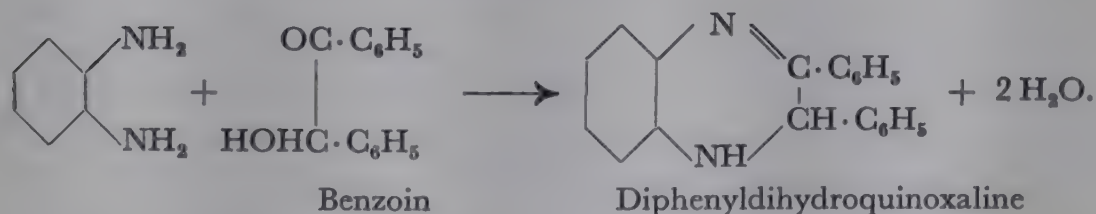
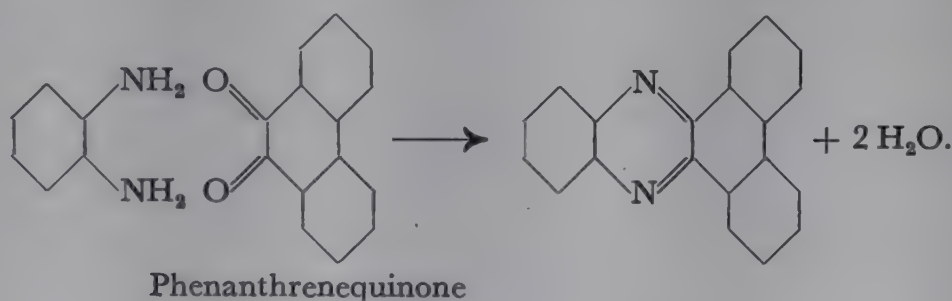
(c) *o*-Phenylenediamine and glyoxal yield quinoxaline:



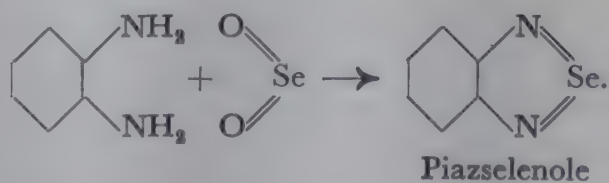
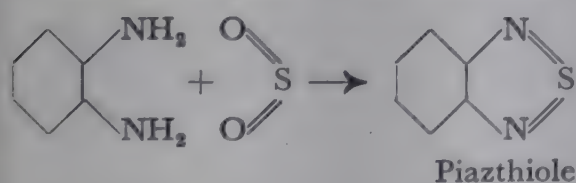
In place of glyoxal, other α -dicarbonyl compounds, such as α -aldehydo-ketones, α -diketones, glyoxylic acid, α -ketocarboxylic acids, and even benzoin (see p. 505) may be used (Hinsberg):



Usually phenanthrenequinone is used for condensations with *o*-diamines. It reacts very smoothly, and the phenazine compounds produced are extremely difficultly soluble, so that phenanthrenequinone is a convenient reagent for *o*-phenylenediamine and its derivatives:

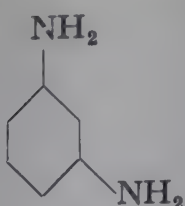


(d) From *o*-phenylenediamine and sulphur dioxide or selenium dioxide peculiar, very stable, heterocyclic compounds have been prepared (Hinsberg) which have been called *piazthioles* or *piazselenoles* (abbreviation for para-diazthiole, "ole" denoting a five-membered ring, which is made up from two nitrogen atoms ("diaz") in "para" position and a sulphur atom ("thio")):



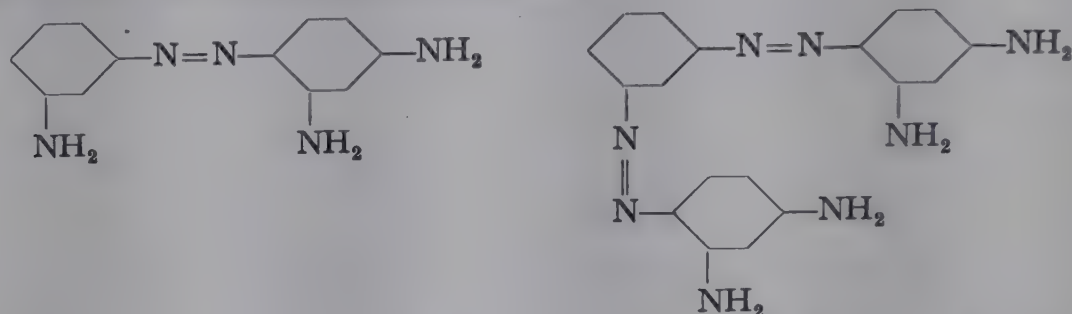
Piazselenole forms yellow salts with mineral acids.

o-Phenylenediamine has a limited technical interest. It is used in the dyeing of hair and furs.

m-PHENYLENEDIAMINE, , is prepared from the readily accessible

m-dinitrobenzene, which is reduced (technically) with iron and hydrochloric acid. It melts at 63°, and boils at 287°.

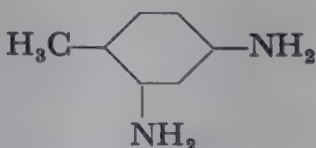
The behaviour of *m*-phenylenediamine towards nitrous acid is characteristic. It is converted by nitrites in acid solution into brown azo-dyes. The mixture of these is met with in commerce as *Bismarck brown*, or *Vesuvian*, and contains, amongst others, the following constituents:




They are produced by the coupling of mono- and bis-diazotized *m*-phenylenediamine with unchanged *m*-phenylenediamine molecules (see p. 487).

On the condensation of aldehydes with *m*-phenylenediamine and its derivatives to give acridine dyes, see Chap. 49.

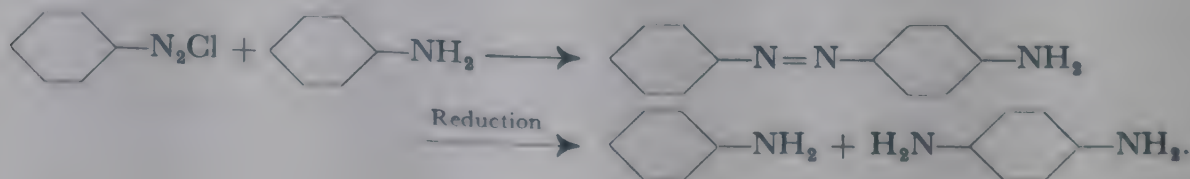
m-Phenylenediamine, and its derivatives containing methylated or phenylated amino-groups are very important for the synthesis of dyes, particularly azo-dyes, and are also used for the development of diazotized dyes on the fibre. *m*-Phenylenediamine also finds limited application as a hair dye, and its hydrochloride is used for the treatment of diarrhoea ("Lentin").

m-TOLYLENEDIAMINE,  m.p. 99°, b.p. 283–285°. This

substance is an important component of dyes (acridine, sulphur, and azo-dyes), and is used as a developer for diazotized dyes.

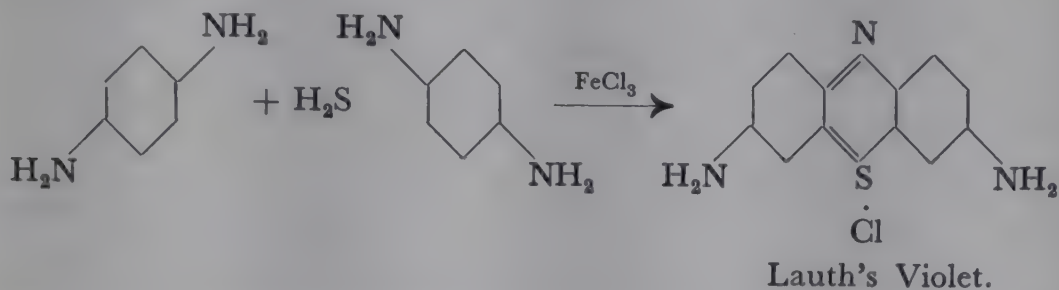
p-PHENYLENEDIAMINE, . This substance is prepared from *p*-nitraniline

by energetic reduction. In industry, however, it is usually made by coupling diazotized aniline with aniline to give *p*-aminoazobenzene (see p. 487) and then reducing this azo-dye. Equimolecular proportions of aniline and *p*-phenylenediamine are thus formed:



p-Phenylenediamine crystallizes in leaflets, melting at 117°; b.p. 267°. It is easily converted by oxidizing agents into *p*-benzoquinone (see p. 576).

The following reaction is characteristic for *p*-phenylenediamine and similar *p*-diamines. The base is dissolved in aqueous hydrogen sulphide solution, and ferric chloride is added, when an intensely blue dye, Lauth's violet, (see Ch. 49 section C) is formed:



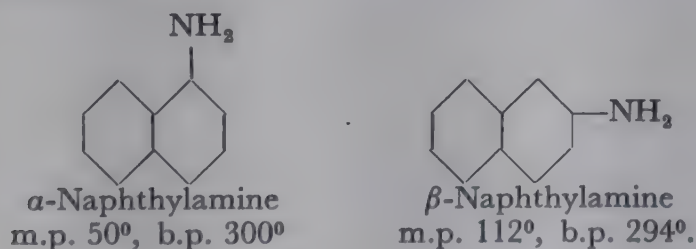
Technically, *p*-phenylenediamine is employed for the synthesis of various dyes, and is used for colouring hair and furs. It is poisonous.

ASYMMETRIC DIMETHYL-*p*-PHENYLENEDIAMINE, $\text{H}_2\text{N}-\text{C}_6\text{H}_4-\text{N}(\text{CH}_3)_2$, m.p. 41°, b.p. 263° (corr.), is a very valuable component of dyes, being employed for the synthesis of various dyes which will be dealt with later. The compound is prepared from dimethylaniline, which is converted by means of nitrous acid into *p*-nitrosodimethylaniline (see p. 455). The latter is reduced, giving *as*-dimethyl-*p*-phenylenediamine:



Aminonaphthalenes

Of the two isomeric monoaminonaphthalenes or *naphthylamines*, the α -compound is obtained by the reduction of 1-nitronaphthalene (see p. 405) with iron and hydrochloric acid, whilst β -naphthylamine on the other hand is obtained by Bucherer's synthesis (see p. 430) from β -naphthol by the action of ammonium sulphite and ammonia:



Both compounds form well-crystallized, stable salts with mineral acids. They are used, particularly the α -isomeride, as coupling components in the synthesis of azo-dyes, and for the preparation of the important naphthylamine-sulphonic acids (see below). α -Naphthol is made from α -naphthylamine.

1 : 5-DIAMINONAPHTHALENE, m.p. 189°, and 1 : 8-DIAMINONAPHTHALENE, m.p. 66°, are used in the preparation of dyes. They are synthesized from the corresponding dinitronaphthalenes.

Aromatic amines with the amino-group in the side chain

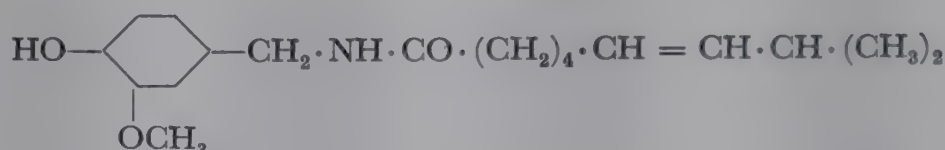
The simplest compound of this class is *benzylamine*, $\text{C}_6\text{H}_5\text{CH}_2\text{NH}_2$, isomeric with the toluidines, but totally different from them in nature. It is a fuming liquid with an ammoniacal smell, which dissolves in water with a strongly alkaline reaction. It boils at 185° . In its whole behaviour it thus resembles the aliphatic amines. The effect of the phenyl radical on the amino-group, which in aniline and its analogues results in a great weakening in basic power, disappears as soon as the amino-group is taken from the nucleus and inserted in the side chain. The benzylamine derivatives alkylated in the amino-group, $\text{C}_6\text{H}_5\text{CH}_2\text{NHR}$ ($\text{R} = \text{CH}_3, \text{C}_2\text{H}_5, \text{C}_3\text{H}_7$), are considerably stronger bases than benzylamine itself.

The methods of preparing benzylamine are also similar to those by which the aliphatic amines are obtained. The compound is usually made by the action of ammonia on benzyl chloride:



Occasionally the reduction of benzonitrile, $\text{C}_6\text{H}_5\text{CN}$, to benzylamine is used.

The active principle of cayenne pepper, or paprika, viz. *capsicin*, is a substituted benzylamine derivative. It has been recognized as vanillylamine acylated by decylenic acid, $\text{C}_9\text{H}_{17}\text{COOH}$, and has the formula



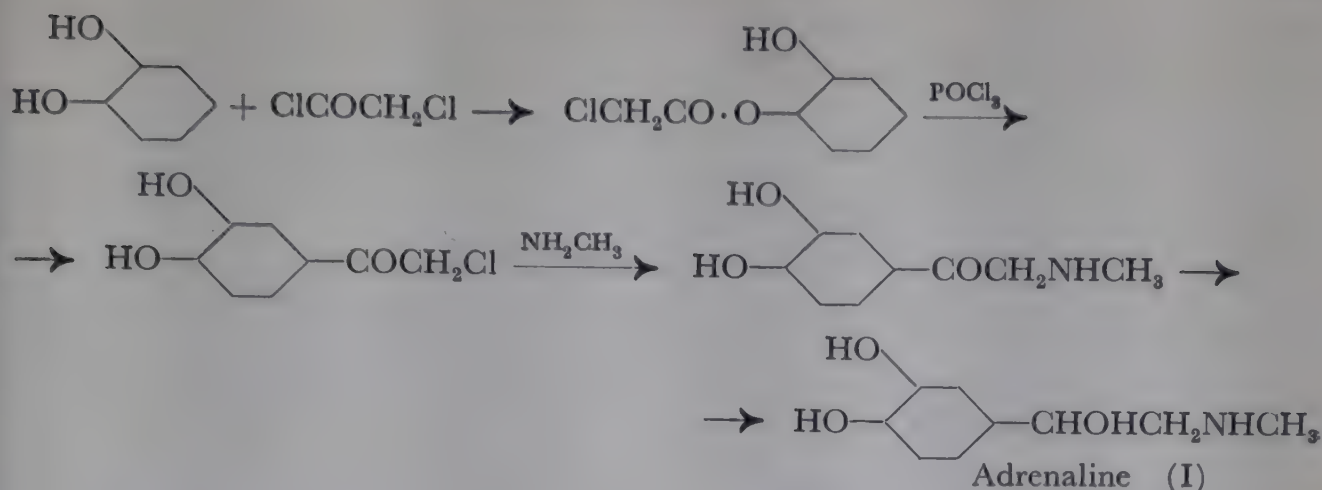
It has also been produced synthetically.

β -PHENYLETHYLAMINE, $\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{NH}_2$. This base has often been encountered in the investigation of decaying protein. It is produced here by the decarboxylation of phenylalanine. It is made synthetically by the reduction of benzyl cyanide, $\text{C}_6\text{H}_5\text{CH}_2\text{CN}$. Several alkaloids, such as ephedrine, hordenine, and tyramine, are derived from it. *Adrenaline*, a substance occurring in the animal organism is especially important. It is a phenylethylamine derivative substituted in the benzene nucleus and in the side chain. The following points may be mentioned in connection with it.

ADRENALINE, $\text{C}_9\text{H}_{13}\text{NO}_3$. It is a hormone of the suprarenal gland and is genetically related to proteins.

Fusion of adrenaline with caustic potash gives protocatechuic acid and pyrocatechol. When boiled with hydriodic acid, methylamine is split off. In addition, an alcoholic hydroxyl group can be detected in the base. These facts make formula I very probable for adrenaline, and it has been confirmed by a simple and straightforward synthesis of the hormone by Stolz:

Pyrocatechol is fused with chloracetic acid and phosphorus oxychloride. The first product of the reaction is pyrocatechol monochloracetate, which rearranges with POCl_3 into 3:4-dihydroxyphenyl chloromethyl ketone. The chlorine of the latter is then replaced by methylamine, and finally, moderate reduction of the ketone with, for example, aluminium amalgam, gives *dl*-adrenaline:

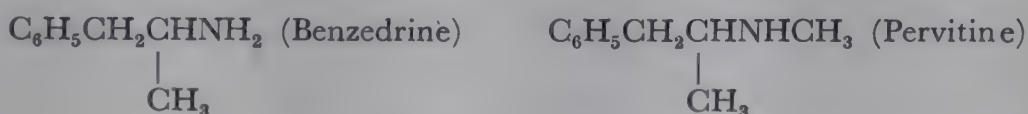


The inactive base may be resolved into the optically active forms by means of the tartrates. Natural adrenaline is lævorotatory ($[\alpha]_D = -50.5^\circ$). It decomposes at 212° .

Adrenaline is widely used in therapeutics. It contracts the blood capillaries and is therefore used in surgery for the anæmization of the location of an operation; some adrenaline is usually added to solutions of anæsthetics (novocaine, etc.). It is also used in the treatment of asthma, hay fever, etc., as it affects the sympathetic nervous system. The action of the base (dilation of the pupils, and action as a weak local anæsthetic) are not of great practical importance. Greater doses cause excretion of sugar in the animal organism (glucosuria).

The adrenaline molecule has been modified chemically in different ways. The oxidation of the alcohol to the ketone, the shifting of the phenolic hydroxyls to different places in the aromatic nucleus and so on, have not led, however, to any increase in the activity of the substance, but usually to a decrease. The replacement of the methylamine residue by an *isopropylamine* group, on the other hand, produces a compound which is more effective in the treatment of asthma.

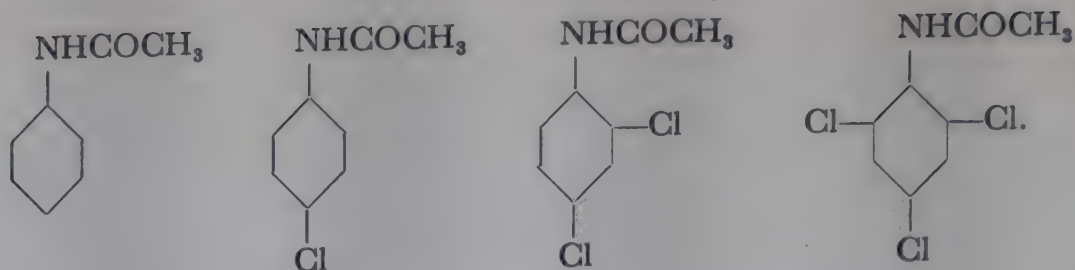
Many β -phenylethylamine derivatives show very pronounced physiological activity, for example the compounds ephedrine and tyramine (q.v.). α -Methyl- β -phenylethylamine and its N-methyl derivative may be mentioned here:



They are powerful central analeptics and affect the blood circulation. They are stimulants, like caffeine, but much stronger and they will waken persons from a deep sleep, even when it is induced by narcotics ("waking amines").

Halogen derivatives of aromatic amines

The presence of the amino-group facilitates the chlorination, nitration, and sulphonation of the aromatic nucleus in the same way as the presence of the hydroxyl group does. The aromatic amines are, in general, readily attacked by the halogens. In order to obtain the simple chlorinated compounds it is necessary to use the acetyl derivatives of the amines. In this way, for example, aniline yields *p*-chloroaniline in addition to some *o*-chloroaniline, the former predominating. The further action of chlorine results in the formation of 2:4-dichloro-, and finally 2:4:6-trichloroaniline (or their acetyl compounds):



m-Chloroaniline is obtained by the reduction of *m*-nitrochlorobenzene.

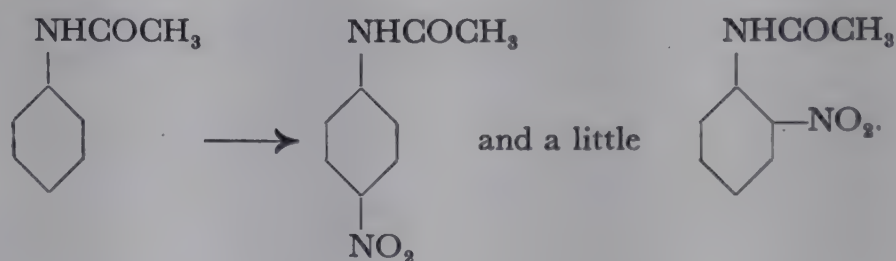
o-Chloroaniline, b.p. 207°; *m*-chloroaniline, b.p. 236°; *p*-chloroaniline, m.p. 70°, b.p. 232°. Their technical use is small.

Halogen atoms standing in the *o*- or *p*-positions to an amino-group weaken the basic character of the amine considerably. On the other hand, halogen in the *m*-position has little effect on the basicity of the amine.

Nitro-derivatives of aromatic amines

If aromatic amines are treated with concentrated nitric acid, oxidation takes place in most cases in addition to the nitration. Nitrophenols are thus often formed. If a nitramine is to be obtained the amino-group must be "protected", and this can be done by acylating it, or carrying out the nitration of the amine in concentrated sulphuric acid.

It depends on the method used and the starting material which position with respect to the amino-group the entering nitro-group takes up. In the nitration of acetanilide, *p*-nitroacetanilide is preferentially formed, together with a little of the *o*-compound:



If aniline is nitrated in concentrated sulphuric acid, however, approximately equal quantities of *m*- and *p*-nitraniline are obtained.

o- and *p*-nitraniline are also readily obtained by heating the corresponding nitrochlorobenzenes (see p. 415) with ammonia, since the chlorine atoms of the latter are activated by the nitro-groups.

The basic properties of the aromatic amines are weakened by nitro-groups in the *o*- and *p*-positions with respect to the NH_2 -group. The effect of an *o*-nitro-group is greater than that of a *p*-group. *m*-Nitraniline, on the other hand, is very little weaker as a base than aniline. The varying basic properties of the nitranilines can be used in their separation.

In the *o*- and *p*-nitranilines the amino-group can readily be replaced by hydroxyl by warming the compound with alkalis. It appears to have been made mobile by the presence of the NO_2 -radical (see p. 415). This hydrolytic elimination of ammonia is particularly easily carried out in the case of 2:4:6-trinitraniline (picramide).

o-NITRANILINE forms orange-yellow needles, m.p. 71°.

m-NITRANILINE forms yellow crystals, m.p. 114°. It is used for the preparation of azo-dyes and *m*-phenylenediamine (see p. 460).

p-NITRANILINE forms yellow crystals, m.p. 147°. It is the starting substance for the preparation of dyes and *p*-phenylenediamine.

2 : 4-DINITRANILINE, yellow crystals, m.p. 176°.

2 : 4 : 6-TRINITRANILINE, picramide, m.p. 188°. For the diazotization of this compound, see p. 473.

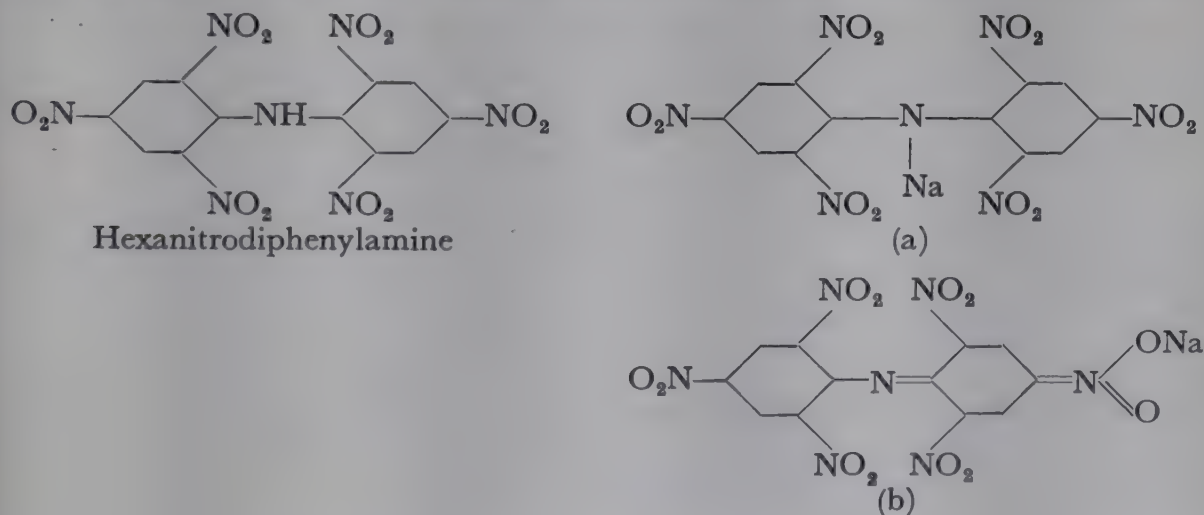
PENTANITRANILINE, made from 3:5-dinitraniline and nitric acid in oleum, m.p. 192°.

NITRONAPHTHYLAMINES have little special interest.

NITRO-DERIVATIVES OF DIPHENYLAMINE. These can be prepared, for example, by fusing together aniline or analogous compounds with (*o*- or *p*-) nitro- or dinitrochlorobenzene:

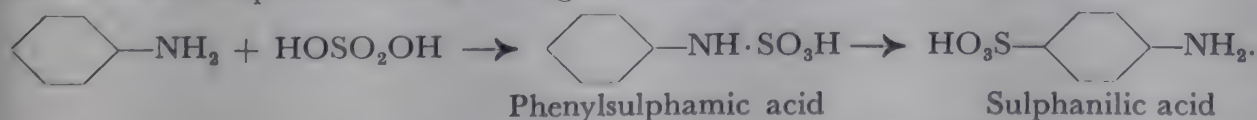


The most important body of this series is hexanitro-diphenylamine, made by nitrating diphenylamine. It is a powerful explosive. Its sodium or ammonium salt is used as a yellow dye for leather and silk, and especially as a light filter for photographic purposes, under the name of *aurantia*. Two tautomeric formulæ, (a) and (b), come under consideration in connection with these salts. Since one red and one yellow series of salts, so-called "chromoisomeric" series, have been found, it is possible that these are the derivatives of the two tautomeric forms.



Sulphonic acids of aromatic amines

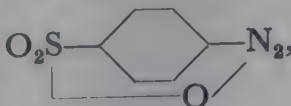
A. Sulphonic acids of aniline. On heating aniline with concentrated sulphuric acid to 200°, the *p*-sulphonic acid, known as SULPHANILIC ACID, is formed. Phenylsulphamic acid is probably formed as an intermediate product, and isomerizes to sulphanilic acid during the course of the reaction:



Sulphanilic acid is an internal salt, in which the sulphonic acid radical has neutralized the amino-group. Sulphanilic acid therefore gives no salts with

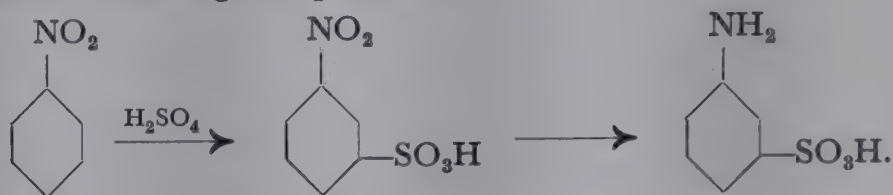
mineral acids. However, the sulphonic acid group can form salts with alkalis.

The compound crystallizes with two molecules of water of crystallization. It dissolves fairly difficultly in cold water. On diazotization it gives diazobenzene-

sulphonic acid, , and it is largely used in the dyestuff industry,

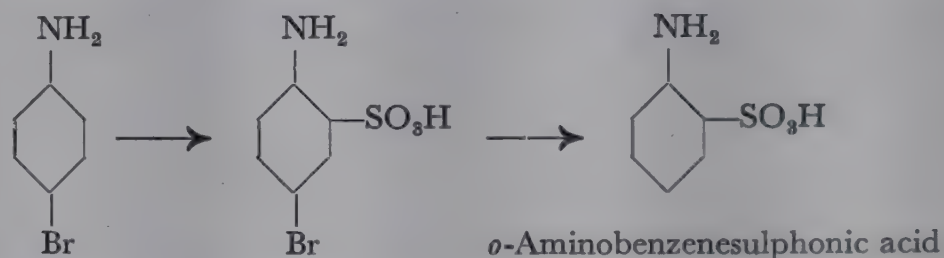
particularly in the diazotized form. The amide of sulphanilic acid is an antiseptic effective against streptococci (Prontalbin). Many derivatives of sulphanilamide have become important as effective chemotherapeutic agents in cases of infectious diseases (e.g. uliron, $(\text{CH}_3)_2\text{NSO}_2 \cdot \text{C}_6\text{H}_4 \cdot \text{NHSO}_2 \cdot \text{C}_6\text{H}_4\text{NH}_2$, in gonococcal diseases). Some important derivatives belonging to this group are mentioned in Ch. 60 and Ch. 61.

m-Anilinesulphonic acid, or METANILIC ACID, is obtained by sulphonating nitrobenzene and reducing the product:



It is used in making Metanil yellow.

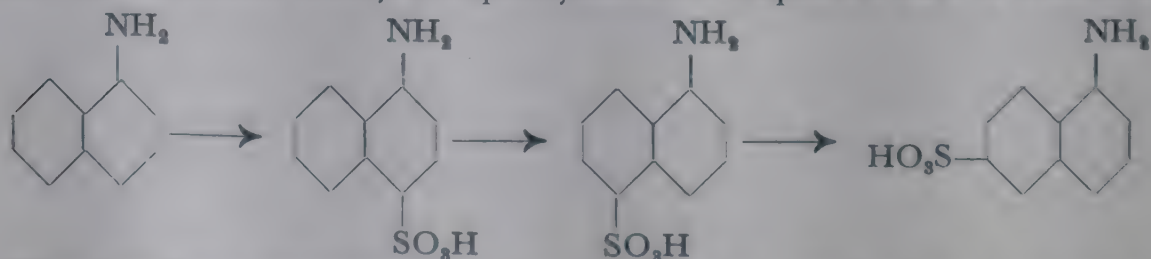
The *o*-isomeride is the most difficult to obtain. *p*-Bromoaniline is sulphonated, and the bromine is then removed by reduction:



It can also be obtained by the action of sulphur dioxide on phenylhydroxylamine ($\text{C}_6\text{H}_5\text{NHOH}$).

B. Sulphonic acids of the naphthylamines. Many mono-, di-, and tri-sulphonic acids which are exceedingly important in the synthesis of dyes, are derived from the two naphthylamines. They are obtained either by sulphonation of the naphthylamines, or by heating the naphtholsulphonic acids with ammonia, or by reduction of nitronaphthalenesulphonic acids.

The course of the sulphonation depends a great deal on the conditions of the reaction (temperature, reaction time, quantity of sulphuric acid used). Thus, by heating α -naphthylamine with sulphuric acid to 180–200°, α -naphthylamine-4-sulphonic acid is first formed, but on longer sulphonation, α -naphthylamine-5-sulphonic acid, and finally α -naphthylamine-6-sulphonic acid is formed:



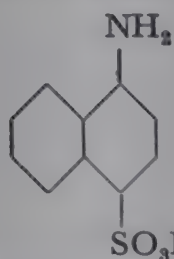
This peculiar phenomenon is due to the fact that at the start all three

sulphonic acids are formed, but that first the 1:4-acid, and then the 1:5-acid are hydrolytically decomposed by the sulphuric acid, so that finally only the 1:6-acid, the most stable of them all, remains.

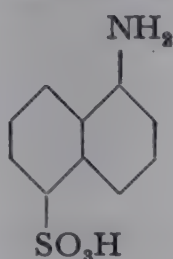
Of the monosulphonic acids of β -naphthylamine, the 2:5-, 2:6-, 2:7-, and 2:8-naphthylaminesulphonic acids are formed by sulphonating β -naphthylamine under varying conditions. β -Naphthylamine-6- and -7-sulphonic acids are usually obtained from the corresponding naphtholsulphonic acids (see p. 446) by treating them with ammonia.

More energetic sulphonation leads to the formation of di- and trisulphonic acids of the naphthylamines.

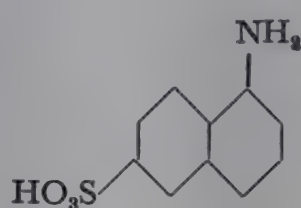
In this text-book we must limit ourselves to mentioning only a few of the more important representatives of the series of naphthylaminesulphonic acids. The number of isomerides known and used technically is fairly large. A noteworthy new use for these compounds has been found in the synthesis of compounds with trypanocidal action (e.g. "Germanine") (see p. 470).



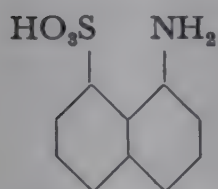
1-Naphthylamine-4-sulphonic acid,
Naphthionic acid



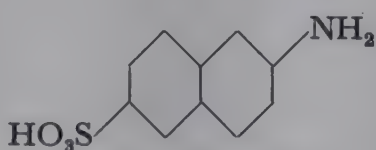
1-Naphthylamine-5-sulphonic acid,
 α -Naphthylamine-sulphonic acid L



1-Naphthylamine-6-sulphonic acid, Naphthylaminesulphonic acid (*Cleve*)



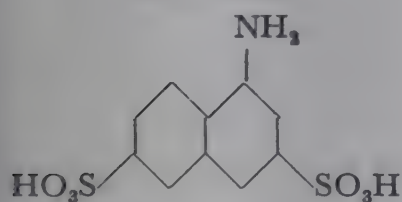
1-Naphthylamine-8-sulphonic acid, Naphthylamine-sulphonic acid S
(*Schöllkopf*)



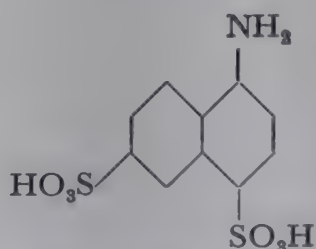
2-Naphthylamine-6-sulphonic acid β or Br
(*Bronner*)



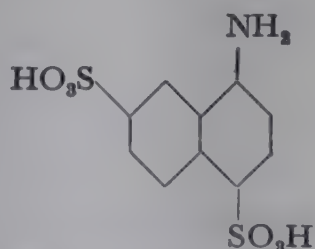
2-Naphthylamine-7-sulphonic acid
F-Acid or δ -Acid



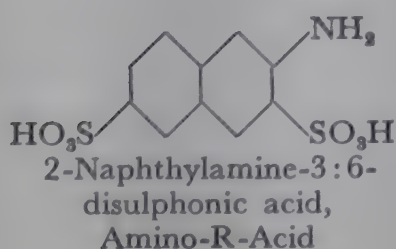
1-Naphthylamine-3:6-disulphonic acid



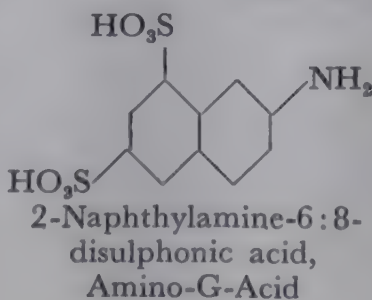
1-Naphthylamine-4:6-disulphonic acid,
Dahl's Acid II



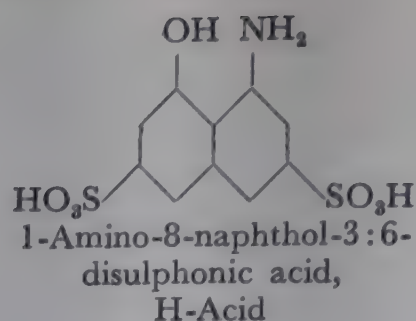
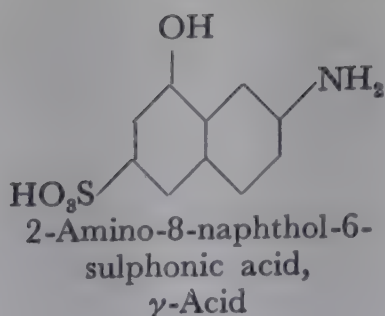
1-Naphthylamine-4:7-disulphonic acid,
Dahl's Acid III



2-Naphthylamine-3:6-disulphonic acid,
Amino-R-Acid



2-Naphthylamine-6:8-disulphonic acid,
Amino-G-Acid



Aminophenols

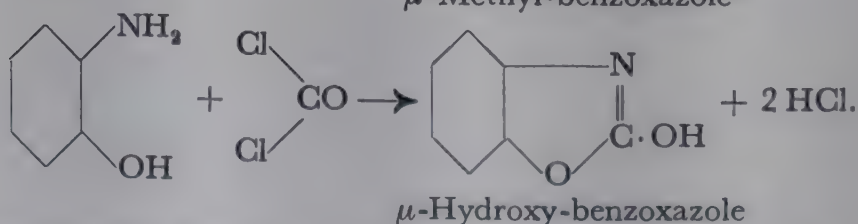
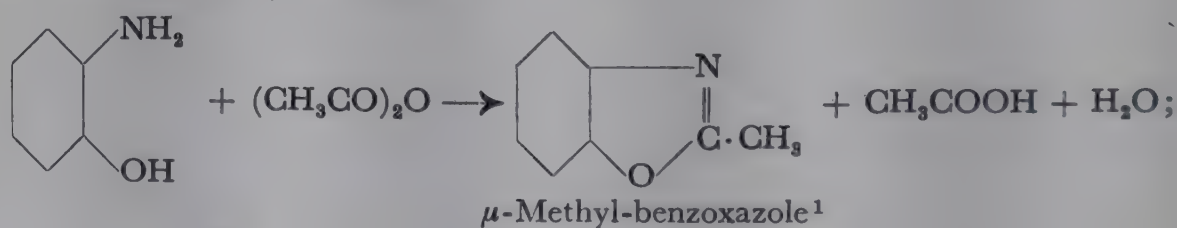
The aminophenols can in general be obtained by the reduction of nitrophenols (see p. 447). Of interest from the theoretical point of view and industrially, is the formation of *p*-aminophenol, which is produced by the isomerization of phenylhydroxylamine under the action of strong sulphuric acid:



In practice, the phenylhydroxylamine is not isolated, but the preparation of this compound is combined with the isomerization process, nitrobenzene being reduced in concentrated sulphuric acid solution, often electrolytically (see p. 452).

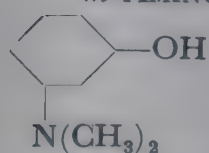
Aminophenols are basic in nature and form salts with mineral acids. Being phenols, they also dissolve in caustic alkalis. Like the dihydric phenols and the diamines, they are readily oxidized, especially in alkaline solution. On this depends their use as photographic developers.

o-AMINOPHENOL, m.p. 174° , tends, like the *o*-diamines, towards ring closure. On treatment with acid anhydrides, and with phosgene, heterocyclic compounds, derivatives of oxazole, are formed:



o-Aminophenol is little used in the synthesis of dyes. On the other hand, it is used, as well as its *N*-methyl derivative, for dyeing hair.

m-AMINOPHENOL, m.p. 123° , and especially its *N*-dimethyl derivative (m.p. 87°) are important starting materials in the preparation of the rhodamine and rosamine dyes (see p. 634).



p-AMINOPHENOL, m.p. 184° , is a component of dyes (especially sulphur dyes, see p. 626), and is also used as a photographic developer (rodinal,

¹ In azoles the CH-group lying between the two hetero-atoms is occasionally called the "meso-group", abbreviated to *ms* or μ .

stabilized with sodium sulphite). N-Methylaminophenol is used under the name "metol" for the same photographic purpose.

The methyl ethers of aminophenols, $C_6H_4(NH_2)OCH_3$, are known as *anisidines*, and the corresponding ethyl ethers as *phenetidines*. According to P. E. Verkade, 4-nitro-2-aminophenol ethers possess extraordinarily great sweetening properties, exceeding those of cane sugar up to 4,000–5,000 times.

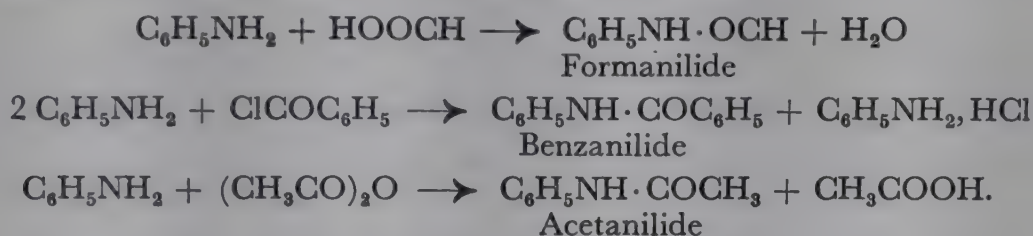
CHAPTER 32

ACID DERIVATIVES OF THE AROMATIC AMINES

Organic acyl derivatives of the aromatic amines

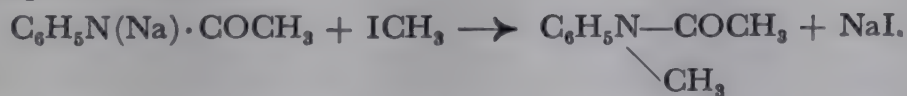
The aromatic primary and secondary amines can be acylated, i.e. the hydrogen of their amino-groups can be replaced by various acid radicals. After the simplest compounds of this type, the derivatives of aniline, they are called "anilides". They have the general formula $Aryl-NH \cdot COR$.

The anilides are prepared by methods which are analogous to those employed in the case of aliphatic compounds. The amines are heated with anhydrous acids, or are treated with acid chlorides or acid anhydrides:



The acylated amines are neutral, they dissolve neither in aqueous alkalis nor in acids, but are hydrolysed on long heating with either, i.e. they are decomposed into amine and acid. Acid hydrolysis usually takes place more readily than alkaline.

If water is excluded the hydrogen atom attached to the nitrogen in acylated amines may be replaced by alkali metals. Water, however, decomposes these sodium or potassium compounds, $C_6H_5N(Na) \cdot COCH_3$, again completely. They react with alkylating agents, and thus form acyl derivatives of secondary mixed aromatic-aliphatic amines:



Some of the simpler acid anilides are characterized by antipyretic and anti-neuralgic properties and are therefore important as drugs. Thus, *acetanilide*, or "antifebrine", $C_6H_5NHCOCH_3$, m.p. 115° , is one such compound. It has, however, undesirable after-effects, and is therefore largely being replaced by more harmless antipyretics.

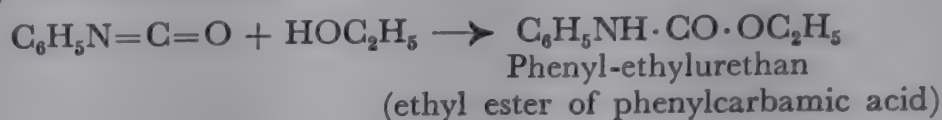
METHYLACETANILIDE, or exalgin, $C_6H_5N \begin{array}{c} | \\ CH_3 \end{array} COCH_3$, m.p. 101° , no longer plays a part in medicine, but is used, like acetanilide, and ethylacetanilide, $C_6H_5N \begin{array}{c} | \\ C_2H_5 \end{array} COCH_3$, in the manufacture of celluloid as a substitute for camphor.

PHENACETIN, or *p*-acetophenetidine, $\text{H}_5\text{C}_2\text{O}-\text{C}_6\text{H}_4-\text{NHCOCH}_3$, melts at 135° , and is a very important, much used, and relatively harmless antipyretic.

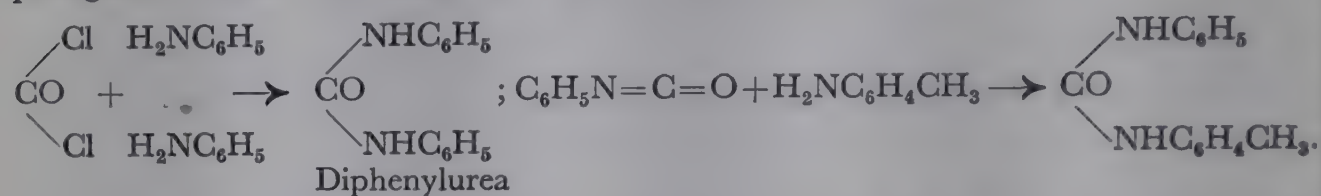
Amongst other simple organic acid derivatives of the aromatic amines those of carbonic acid must be mentioned.

The true *carbamic acids*, $\text{R}\cdot\text{NH}\cdot\text{COOH}$, are only in rare cases more or less stable (e.g. in the case of certain polyamines), and even then only in the form of their metal salts. On the other hand, their esters, the *urethans*, and their amides, the simple and mixed *ureas*, are well-known.

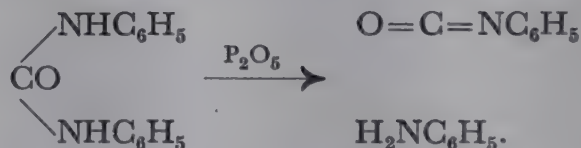
The urethans are usually prepared from the aryl *isocyanates*, e.g. phenyl *isocyanate*, by the action of alcohols:



Aromatic derivatives of urea are prepared either from the amines and phosgene, or from an amine and an aryl *isocyanate*:

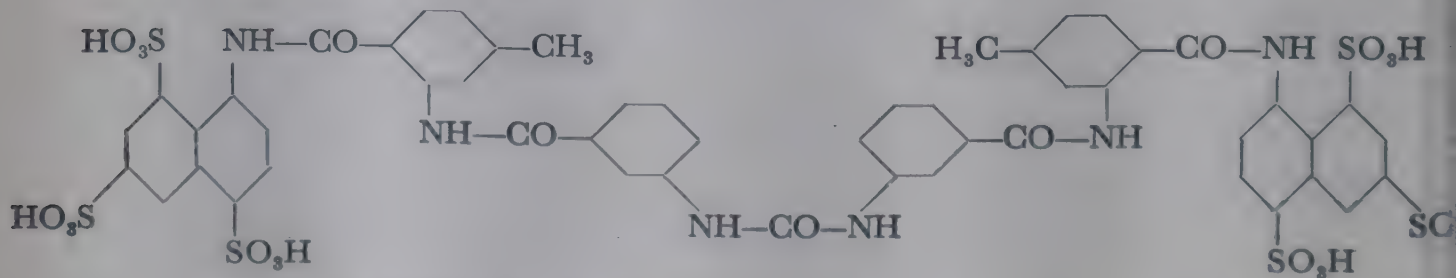


Phenylurethan melts at 52° , and is readily hydrolysed. *Diphenylurea*, or *carbanilide*, is characterized by its great stability. It melts at 235° , and boils at 260° . On distillation with phosphorus pentoxide it is partly decomposed into aniline and phenyl *isocyanate*:



Various phenylated derivatives of urea have a sweet taste, e.g. the symmetrical dimethyldiphenylurea, $\text{C}_6\text{H}_5(\text{CH}_3)\text{N}\cdot\text{CO}\cdot\text{N}(\text{CH}_3)\text{C}_6\text{H}_5$ (m.p. 121°), and particularly phenetidineurea, $\text{C}_2\text{H}_5\text{O}-\text{C}_6\text{H}_4-\text{NHCONH}_2$, which is frequently used as a sweetening substance under the name *dulcine*. It tastes 200 times sweeter than cane sugar, but is only slightly soluble in water. It melts at $173-174^\circ$.

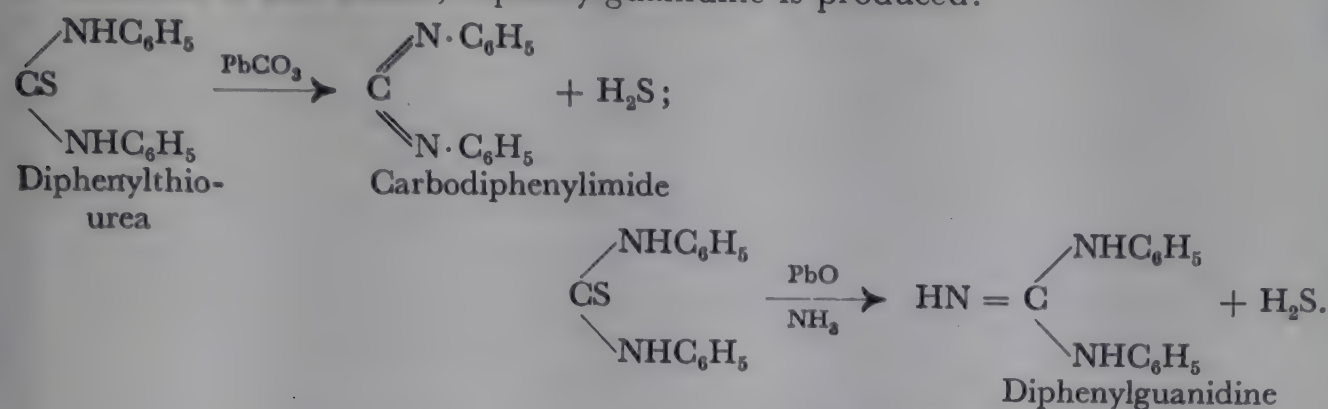
Complex aromatic derivatives of urea have come into prominence as drugs for trypanocidal diseases. The best substance in this group, the so-called "Bayer 205", or "*Germanine*" (R. Kothe, O. Dressel) has the following constitution:



Its activity exceeds that of all previously known trypanocidal substances.

Symmetrical *diarylthioureas* are readily formed by heating aromatic amines with carbon disulphide (see p. 454). *Diphenylthiourea*, or thiocarbanilide, forms very stable crystals, almost insoluble in water, melting at 151° . It is the starting

substance in the Sandmeyer synthesis of indigo (see p. 571). On heating with lead carbonate, hydrogen sulphide is evolved, and carbodiphenylimide is formed. If ammonia is also added, diphenylguanidine is produced:



Inorganic acid derivatives of amines

1. Thionylamines, $\text{Aryl}\cdot\text{N}=\text{SO}$.

Compounds of this composition are formed from aromatic primary amines and thionyl chloride. They are yellow, unstable liquids.

2. Sulphamic acids, $\text{Aryl}\cdot\text{NH}\cdot\text{SO}_3\text{H}$.

Aromatic sulphamic acids are formed from amines and chlorosulphonic acid or sulphuric acid:



They are therefore intermediate products in the preparation of the sulphonic acids of the amines. They are purified by means of their barium salts. They are also often obtained in the reduction of aromatic nitro-compounds by means of sodium hydrosulphite.

A characteristic property of many sulphamic acids is their rearrangement into aminosulphonic acids which occurs when the acids, or their salts, are heated. The sulphonic acid group enters the *p*-position preferentially, but if this is occupied, the *o*-position:



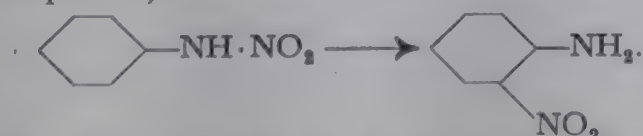
On boiling with water the sulphamic acids are hydrolysed to amines and sulphuric acid.

3. Nitranilides, $\text{Aryl}\cdot\text{NH}\cdot\text{NO}_2$.

There are various methods of preparing nitranilide, $\text{C}_6\text{H}_5\text{NHNO}_2$ (Bamberger). The simplest is the action of highly concentrated nitric acid and acetic anhydride on aniline at low temperatures:



The compound crystallizes well, melts at 46° , and explodes weakly on heating to 100° , with evolution of nitrogen. It is unstable, and by the action of light, warming, or treatment with acids, isomerizes to nitraniline (preferentially *o*-, but with some of the *p*-compound):



This isomerization corresponds to the above-mentioned transformation of sulphamic acids into sulphonic acids of the amines.

On the other hand, nitranilide shows greater stability in alkalis, in which it dissolves with salt formation. The salts must be represented by one of the following tautomeric forms, in which nitranilide can react:



A methyl derivative derived from formula I can be made from the sodium salt of nitranilide and methyl iodide. It melts at 39° and can isomerize into *o*- and *p*-nitromethylaniline. It must therefore have the structure III:

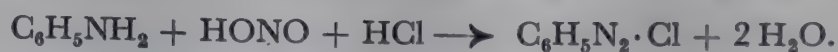


An isomeric methyl derivative, IV, is formed from the silver salt of nitranilide and methyl iodide. It is a yellow liquid, very unstable, and decomposes completely within a few hours.

4. Nitrous acid derivatives of aromatic amines. Diazonium salts.¹

The products of the action of nitrous acid on acid solutions of primary aromatic amines, the *diazonium salts*, discovered by P. Griess, are the most important derivatives of aromatic bases. Their importance cannot easily be over-estimated, as they are indispensable starting materials for the preparation of various other derivatives, as well as the parent substances of the large and important class of azo-dyes.

The preparation of diazonium salts from primary aromatic amines is called "*diazotization*". It is carried out by acting upon a solution of an amine in a mineral acid with sodium nitrite, and proceeds according to the equation:



Definite conditions must be observed for the successful performance of a diazotization. Equimolecular quantities of nitrite and amine are used, and the mineral acid should be in excess, at least 2 to 2½ equivalents being present. If the quantity of acid is smaller, the amine and nitrous acid react in part in another way, with formation of diazoamino compounds, e.g. $\text{C}_6\text{H}_5\text{N}=\text{N}\cdot\text{NHC}_6\text{H}_5$ (see p. 481). On account of the readiness with which most diazonium salts decompose, which increases rapidly with increasing temperature, the diazotization is always carried out in the cold, between 0° and 5°.

In this way, aqueous solutions of diazonium salts are produced. Caution is necessary in their isolation, since many dry diazonium salts are exceedingly explosive. However, their further reactions do not make necessary a separation in the dry form in most cases. Nevertheless, should it be necessary to prepare the solid salts, esters of nitrous acid (amyl nitrite, ethyl nitrite) are allowed to act upon solutions of the amine in alcohol or glacial acetic acid. The diazonium salts are difficultly soluble in these liquids and are precipitated in the solid form (sometimes only after adding ether).

There are, however, a few diazonium salts, such as that derived from sulpha-

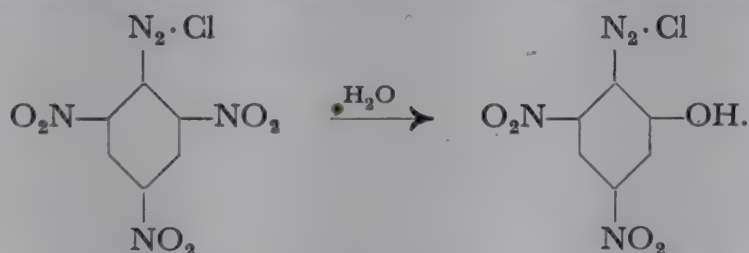
¹ See A. HANTZSCH and G. REDDELIEN, *Die Diazoverbindungen*, Berlin, (1921).

nilic acid, which are difficultly soluble also in water and which crystallize from concentrated solutions.

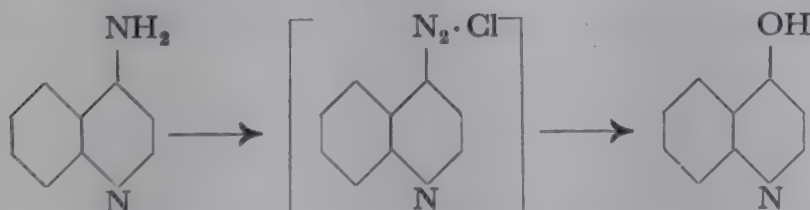
Some amines, particularly those of which the basic nature has been considerably weakened by the presence of negative groups, such as is the case with 2:4-dinitroaniline, and whose salts are completely, or to a large extent, hydrolysed in aqueous solution, are not diazotized smoothly or with a good yield. In these cases the amine is dissolved in concentrated sulphuric acid, and solid sodium nitrite or "nitrosylsulphuric acid", a solution of nitrous acid in concentrated sulphuric acid, is added. Under these circumstances the diazotization proceeds normally.

In another method, due to Witt, the difficultly diazotizable amine is added to concentrated nitric acid, and then the equivalent amount of a reducing agent, e.g. potassium metabisulphite, is added. This reduces the calculated quantity of nitric acid to nitrous acid, and the latter diazotizes the amine present. After dilution with ice, an aqueous solution of the diazonium salt is obtained. This process is recommended, for example, for the diazotization of 2:4-dinitroaniline, or 3:5-dichloro-4-aminophenylarsonic acid. Some amines which are difficult to diazotize (e.g. *o*- and *p*-aminophenols) are more completely diazotized in the presence of stannous chloride.

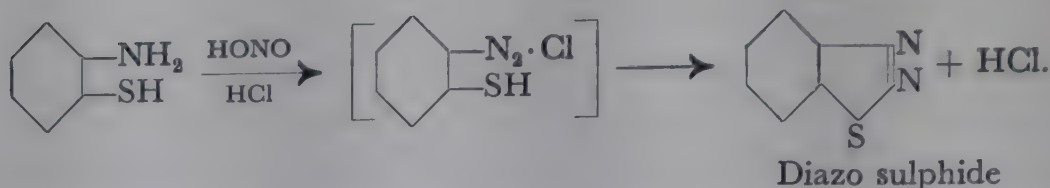
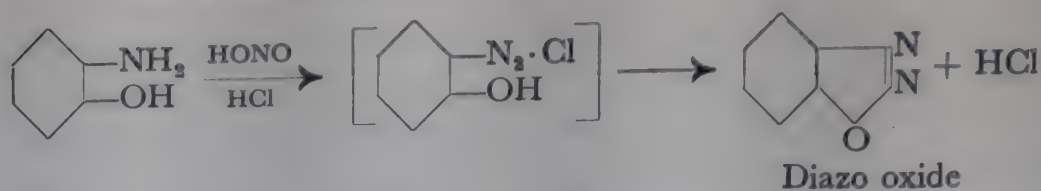
Picramide (2:4:6-trinitroaniline) and analogous polynitroamines were formerly regarded, until the year 1920, as being impossible to diazotize. Misslin has, however, shown that the older failures were essentially due to the fact that the loosening and eliminating effect of the diazonium salt group on substituents in the *o*-position, has not been fully taken into account. If picramide is dissolved in glacial acetic acid, and nitrosylsulphuric acid dropped in in the cold, the amine is diazotized. The solution must not, however, be diluted with water, but must be used as such for further reactions (coupling reactions), since water reacts with this diazonium salt almost instantly with elimination of one nitro-group



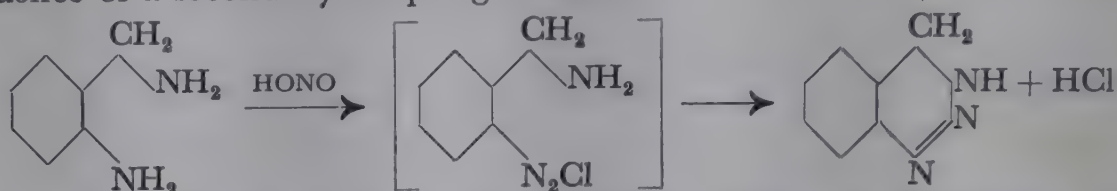
In various cases the diazotization proceeds abnormally, and instead of the expected diazonium salts, secondary transformation products are obtained. Quite often phenols are formed. They owe their origin to the instability of the respective diazo-compounds, or their ready hydrolysis. An example of this is the diazotization of γ -aminoquinoline, which gives γ -hydroxyquinoline:



In other cases the diazonium group reacts in the nascent state with hydroxyl or SH groups in the *o*-position. Under these conditions the difficultly soluble "diazo oxides" or "diazo sulphides" are obtained instead of the diazonium salts:

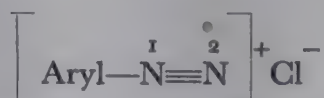


o-Amino-benzylamine is also converted into a closed-ring compound in consequence of a secondary coupling reaction:



The simple diazonium salts are colourless, crystalline compounds, which explode when heated or struck, but are quite harmless in solution. They should therefore never be dried in large quantities. They are usually readily soluble in water, difficultly soluble in alcohol and glacial acetic acid, and quite insoluble in ether.

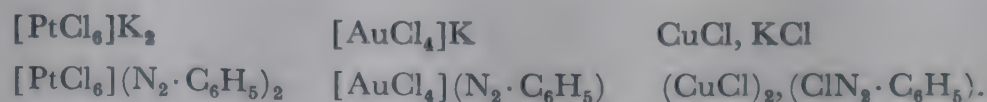
The salt-like nature of these compounds is evident. They can best be compared with the ammonium or alkali-metal salts. Like the latter they are readily soluble in water, giving a neutral solution. On the other hand, aqueous solutions of the diazonium carbonates react alkaline, like solutions of sodium or ammonium carbonate, on account of hydrolysis. Solutions of diazonium salts conduct electricity. Determinations of the molecular weights of the salts dissolved in water give values only about half as great as those required by the formula RN_2X . These phenomena lead to the conclusion that the diazonium compounds are ionized in aqueous solution, like alkali-metal salts. By analogy with the formulæ of the ammonium salts, they are therefore formulated as



the nitrogen atom 1 being considered to be the bearer of the positive charge. It plays the same part as the coordinately tetravalent nitrogen atom of ammonium compounds.

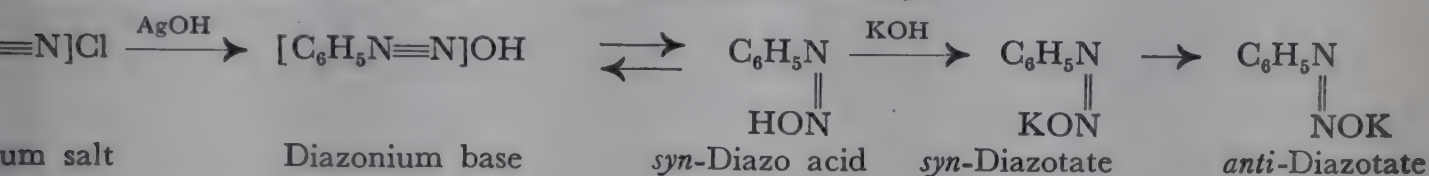
(The older Kekulé formulation, $\text{RN}=\text{N}\cdot\text{Cl}$, has now been generally discarded.)

The similarity between ammonium and diazonium salts is also evident in many chemical reactions. Thus, both furnish difficultly soluble perchlorates with perchloric acid, and form analogous double compounds with PtCl_4 , AuCl_3 , and CuCl :

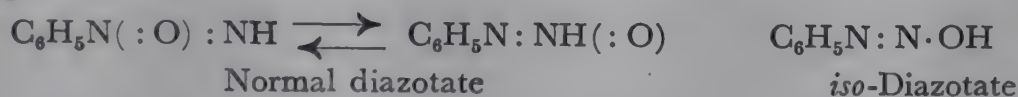


Also the phenomenon of perhalide formation, which is characteristic of the alkali-metal halides, is given by diazonium halides. Hantzsch has prepared many compounds of the type $[\text{C}_6\text{H}_5\text{N}_2]\text{X}_3$, where X may be the same or different halogen atoms (Cl, Br, I), e.g. $[\text{C}_6\text{H}_5\text{N}_2]\text{I}_3$, $[\text{C}_6\text{H}_5\text{N}_2]\text{ClBr}_2$, etc.

ACTION OF ALKALIS ON DIAZONIUM SALTS. Just as ammonium hydroxide is formed when alkalis act upon ammonium salts, so strongly alkaline solutions, which contain "diazonium bases", are obtained from diazonium chlorides and silver hydroxide, or from diazonium sulphates and an equivalent quantity of barium hydroxide. These are, however, fairly unstable, and isomerize readily to the *normal diazotates* (*syn*-diazotates). These relationships are made even more complicated by the fact that there is a series of salts isomeric with the normal diazotates, known as the *iso*- or *anti*-diazotates, which are formed by the isomerization of the normal diazotates on warming with alkali. According to Hantzsch the isomerism of the normal and *iso*-diazotates is due to steric causes. Just as the substituents at an ethylenic linkage may be arranged in *cis*- and *trans*-positions with respect to the double bond (see p. 48), so substituents at the nitrogen double bond are thus believed to be arranged differently in space. They may both lie on the same side, or on different sides of the double bond. In the *syn*-diazotates they are in the *cis*-position (according to Hantzsch), in the *anti*-diazotates in the *trans*-position, and the transformation of the diazonium salts into the isomeric diazotates can accordingly be expressed by the following scheme:



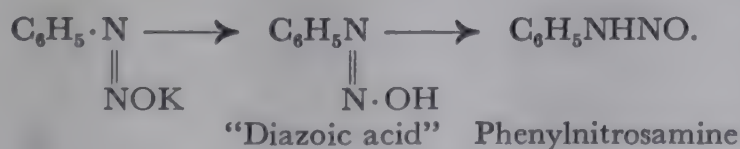
In contrast to the view of Hantzsch, Angeli regards the diazotates and *iso*-diazotates not as stereoisomerides, but as structural isomerides, as shown by the following formulæ:



The normal diazo-hydrates can act as oxidizing agents in alkaline solution, converting, for example, ferrous salts into ferric salts, hydroquinone into quinone, and alcohols into aldehydes. Angeli regards this as support of his view that the normal diazo-hydrates are N-oxides.

Other investigators have put forward similar views, which they support particularly by the fact that the ultra-violet absorption spectra of the two compounds are totally different. According to determinations by Sviatoslawski the *iso*-diazotates have a higher energy content than the normal diazotates.

Addition of the calculated quantity of mineral acid to the *anti*-diazotate gives the free diazoic acid. This is, however, very unstable, and isomerizes to phenyl-nitrosamine:



There is therefore a tautomeric relationship between phenylnitrosamine and the diazoic acid, as exists between the nitro-compounds and their "nitronic acids", or between the nitranilides and their *aci*-forms.

In all these cases the salts are derived from the *aci*-form.

By the addition of excess mineral acid the diazotates are reconverted into diazonium salts.

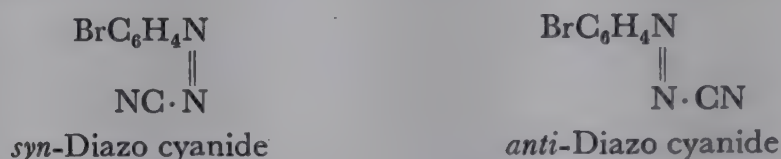
Substitution of the diazo-group by other radicals. The *syn*- and *anti*-diazotates are, according to Hantzsch, members of a large class of compounds, which are called *syn*- and *anti*-diazo compounds. They correspond to the formulæ:



where X is a negative radical (CN, SO₃H, Cl, I, AsO₃H₂, etc.).

They are formed from diazonium salts under various conditions to be described later.

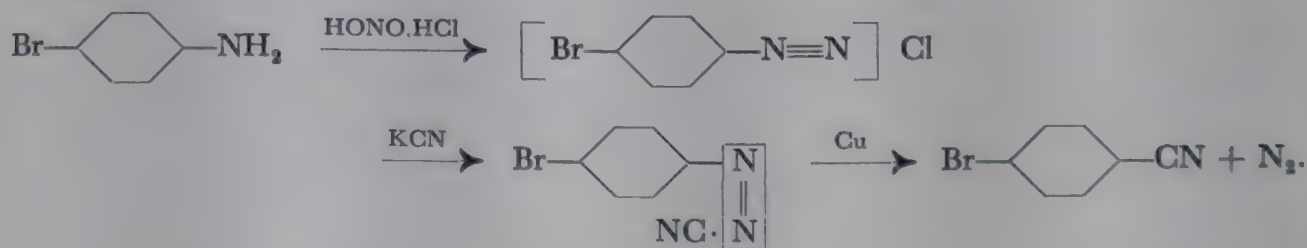
Most of the *syn*-diazo-compounds are, however, so unstable that they cannot be isolated, and their intermediate formation must be inferred from the products of their further reactions. In a few cases it is possible to isolate them. Thus, a yellow compound, bromobenzenediazo cyanide, BrC₆H₄N=N·CN, is produced from *p*-bromobenzenediazonium chloride and potassium cyanide. In the presence of copper powder it breaks down into bromobenzonitrile, with evolution of nitrogen. This diazo cyanide is not very stable (m.p. 42°); it changes in a short time into a stable isomeric form (m.p. 120°), which gives off no nitrogen when treated with copper powder. The two isomers are mostly regarded as *syn*- and *anti*-diazo cyanides:



The stable compound was formerly considered to be the *anti*-form; recently, the reverse view is also held which is based on dipole measurements.

According to Hodgson and Marsden, the *syn*- and *anti*-diazo cyanides are not stereoisomers but structural isomers, the former having the formula RN=N·CN, and the latter the structure RN=N·N⁺≡C⁻. This conception, however, has been opposed by Anderson, La Fèvre, and Savage.

From the above it follows that the amino-group of *p*-bromoaniline can be replaced by the CN-group through the diazonium salt, and the *syn*-diazo-compound:

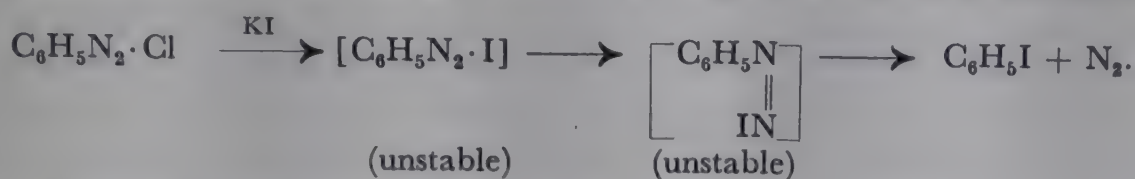


Analogous replacement reactions — “*diazo reactions*” — can be carried out in many other cases in which the isolation of the *syn*-diazo-compounds has not been possible. They were observed in part already by Griess, but were more thoroughly investigated by later workers, particularly Sandmeyer, and have been so worked out and developed that they have become of great preparative importance. Whenever it is desired to replace the primary aromatic amino-groups by other radicals, they are usually used.

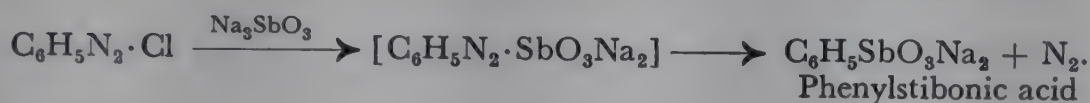
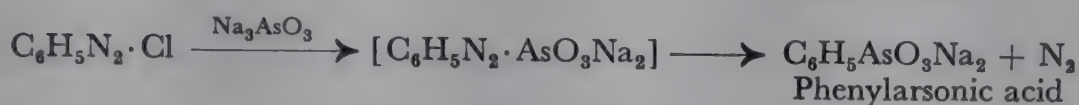
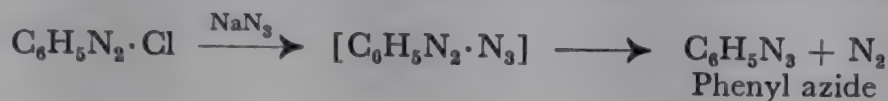
The ease with which the diazonium salt group —N₂·X can be replaced by other radicals varies a great deal from type to type and depends in the first

instance upon the nature of the negative ion X. There are diazonium salts which are so unstable that their isolation under ordinary conditions is completely impossible, because they immediately decompose into nitrogen and a substituted benzene, probably through the *syn*-diazo-compounds (see above). This happens, for example, when X is —I, —N₃, —AsO₃H₂, —SbO₃H₂.

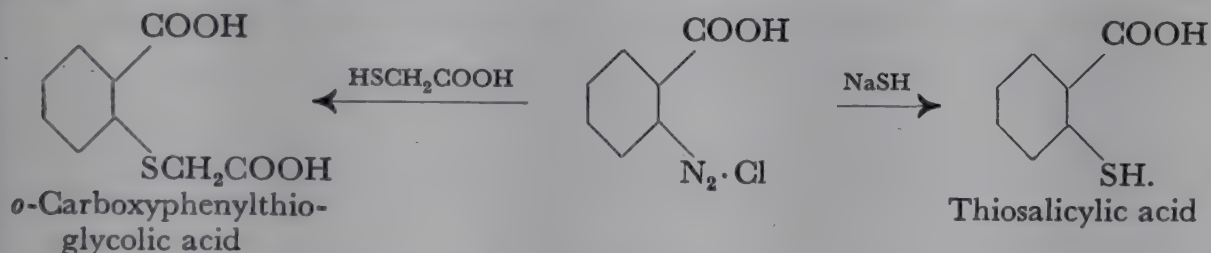
If, therefore, potassium iodide is allowed to react with a benzenediazonium salt, iodobenzene separates out at once, and nitrogen is evolved at the same time:



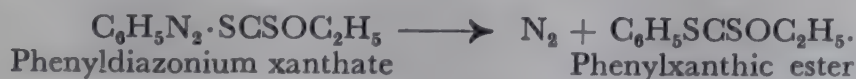
Similarly, aromatic *azides*, *arsonic acids*, and *stibonic acids* may be prepared:



Similar reactions take place when diazonium salts are treated with sodium hydrogen sulphide, or thioglycolic acid, even at ordinary temperatures:



The diazonium *xanthates*, $[\text{R}\cdot\text{N}_2]\text{SCSOC}_2\text{H}_5$, are more stable, and can be isolated at low temperatures. On account of their explosive properties they are hardly ever produced in large quantities, but are decomposed as soon as they are formed giving nitrogen and xanthate esters:



This is carried out practically by allowing potassium xanthate to act upon a solution of benzenediazonium chloride at a temperature of 60–70°, at which the decomposition into nitrogen and the xanthate ester takes place. The latter are used for the preparation of thiophenols.

In several cases where the negative ion X of the diazonium salt is some other than the group just mentioned, its introduction in place of the diazonium salt group is not always successful, even at higher temperatures. Thus, if an aqueous solution of benzenediazonium chloride or benzenediazonium sulphate is heated, no chlorobenzene, or benzenesulphonic acid is formed; the reaction

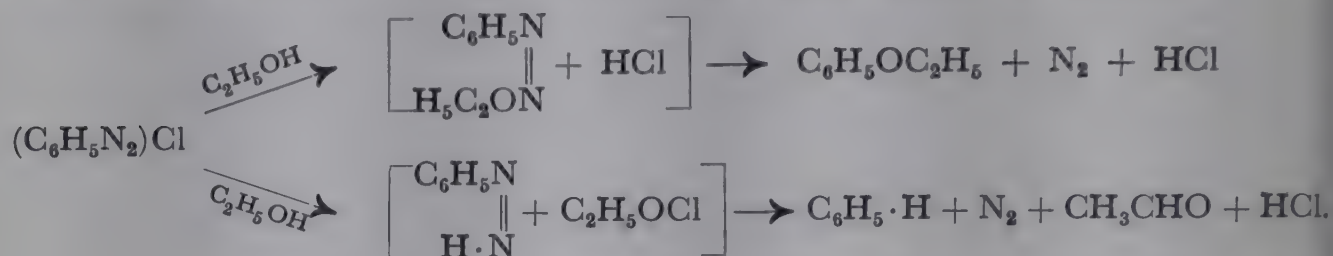


does not take place. Instead, the chief thing that happens is the substitution of

the diazonium group by hydroxyl, i.e. *formation of phenol*. The mechanism of this reaction, which is a very important synthesis of phenol, is given by the following scheme:



Also, when benzenediazonium chloride is heated in *alcoholic* solution, chlorobenzene is not formed. The reaction products are benzene and phenetole. Their formation is readily explained on the assumption that these too have been formed through very unstable *syn*-diazo-compounds, which cannot be isolated:



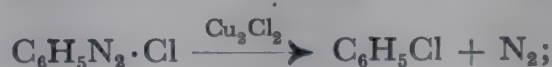
This reaction makes it possible to replace the aromatic amino-group by hydrogen, and it is often used for this purpose. In addition to benzene, acetaldehyde is formed, as the equation shows.

A newer method for the substitution of the diazonium group by hydrogen consists in the action of zinc dust on the diazonium salt, suspended in alcohol or acetone and stabilized by naphthalenedisulphonic acids (see p. 496) (Hodgson and Marsden). By this method the hydrocarbons can be obtained in quantitative yields.

Diazotized amines are also often very smoothly deaminated by the action of copper oxide. The amine solution is diazotized in glacial acetic acid with sodium nitrite and sulphuric acid, after which it is stirred into a suspension of copper oxide and alcohol.

Sandmeyer showed that the decomposition of the diazonium salts can be made to take place according to the equation: $\text{C}_6\text{H}_5\text{N}_2 \cdot \text{X} \longrightarrow \text{C}_6\text{H}_5\text{X} + \text{N}_2$, also in cases such as those mentioned above, if certain catalysts are added to the diazonium salt. In this way the diazo-group can be replaced by:

(a) *chlorine* by the addition of cuprous chloride (Sandmeyer) or finely divided copper powder (Gattermann) to a solution of benzenediazonium chloride:



(Instead of Cu_2Cl_2 , the reaction may also be catalysed, under certain conditions, by FeCl_3 or CuCl_2 .)

(b) *bromine* by adding potassium bromide and cuprous bromide to a solution of benzenediazonium sulphate:



(c) *cyanogen* by treating the benzenediazonium salt solution with potassium cuprocyanide $[\text{Cu}(\text{CN})_4]\text{K}_3$:



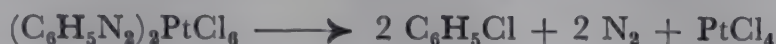
(d) the *isocyanate radical*, $-\text{NCO}$, by adding potassium cyanate and copper powder to a solution of a diazonium compound.

(e) the *thiocyanate group* $-\text{SCN}$, by using cuprous thiocyanate as catalyst:



(f) the *nitro-group*, $-\text{NO}_2$, (preparation of nitro-compounds) by the addition of sodium nitrite and cuprous oxide. This reaction takes place particularly smoothly when the diazonium salts are first converted into aryldiazonium cobalt-nitrites, $(\text{RN}_2)_3\text{Co}(\text{NO}_2)_6$, and the latter decomposed by CuO and CuSO_4 (Hodgson and Marsden). The decomposition of solid diazo sulphonates in concentrated aqueous sodium nitrite solution, by heating in the presence of cupro-cupric sulphite, also leads to the same result.

The action of these catalysts is probably due to the fact that they combine with the diazonium salts to give double compounds, e.g. of the type Cu_2Cl_2 , $\text{ClN}_2\text{C}_6\text{H}_5$, which then undergo decomposition as described above. The analogous platonic chloride-diazonium chloride double salts, $(\text{C}_6\text{H}_5\text{N}_2)_2\text{PtCl}_6$, mentioned above, also break down on heating in the dry state (mixed with sodium chloride) giving chlorobenzene, nitrogen, and platonic chloride:

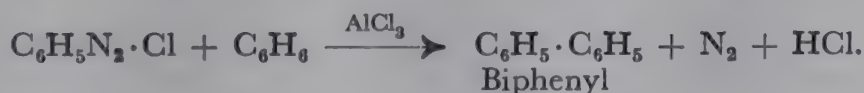


Ferric chloride double salts show a similar decomposition in concentrated hydrochloric acid.

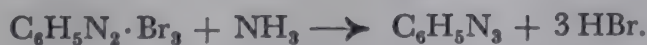


For the catalytic decomposition of *p*-bromophenyldiazo cyanide by copper powder, see p. 476.

The possibilities of the use of diazonium salts for synthetic purposes are not limited to the above examples. These substances can, for example, be used for the synthesis of *multinuclear hydrocarbons*. If the dry diazonium salts are allowed to act upon aromatic hydrocarbons in the presence of aluminium chloride, a new hydrocarbon is produced, the synthesis recalling the Friedel-Crafts reaction:

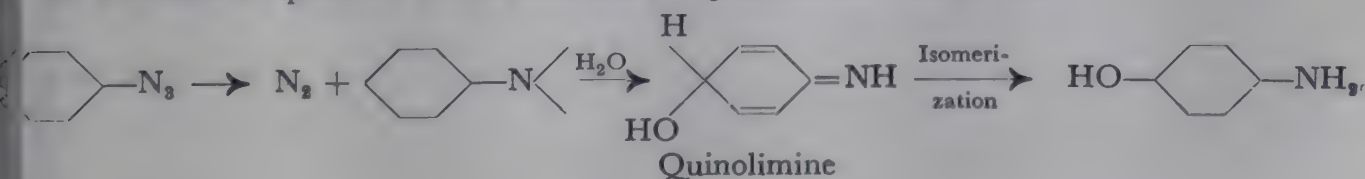


The action of ammonia on the diazonium perhalides (see p. 474) is very peculiar. *Diazobenzene-imines* (aryl azides), the aromatic derivatives of hydrazoic acid, are formed:



For the preparation of the aryl azides by the action of diazonium salts on sodium azide, see p. 477.

Diazobenzene-imine is a yellow oil, which explodes on heating. It is reduced by stannous chloride at low temperatures to diazobenzene-amine, $\text{C}_6\text{H}_5\text{N} = \text{N} \cdot \text{NH}_2$, whilst on heating with dilute sulphuric acid it gives *p*-aminophenol. According to Bamberger an intermediate product in this reaction is "quinolimine" (cf. p. 582).



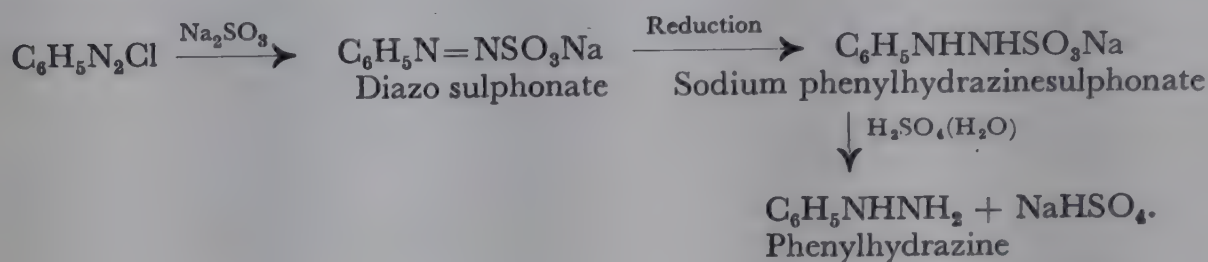
Reduction and oxidation of diazonium salts. *Moderate reduction* of the diazonium salts gives *aromatic derivatives of hydrazine*, and is used as a method of preparing these compounds. It can be carried out in two different ways:

(a) by Victor Meyer's method, in which the diazonium salt solution is mixed with a solution of stannous chloride in hydrochloric acid at low temperatures:



The hydrochloride of the arylhydrazine is formed directly.

(b) by E. Fischer's method. The reaction products of alkali-metal sulphites and diazonium salts, the *diazo sulphonates* (these have constitutions analogous to those of the diazotates and diazo cyanides, and like them occur in *syn*- and *anti*-forms), are reduced with zinc dust and acetic acid, or with sulphurous acid. They are thus converted into salts of arylhydrazinesulphonic acids, from which the sulphonic acid group can be eliminated by heating with dilute sulphuric acid:



The primary arylhydrazines as well as the unsymmetrical diarylhydrazines are important reagents for the carbonyl group. They combine with aldehydes and ketones to give, like their aliphatic analogues (q.v.), hydrazones and osazones which, however, are usually more difficultly soluble and crystallize better than those made from aliphatic hydrazine derivatives. *Phenylhydrazine* particularly is a very common reagent. As a derivative of hydrazine, it possesses powerful reducing properties, and forms tabular crystals, melting at 23° , and it boils at 241° . It slowly changes in the air. It is poisonous, and produces eczema in some people.

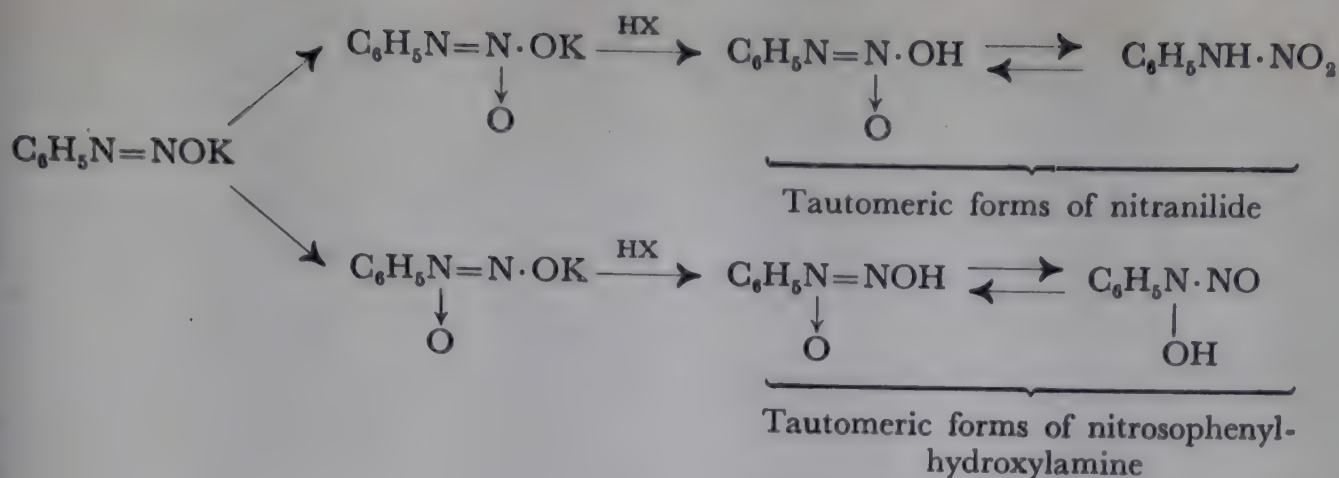
Phenylhydrazine is also used for the synthesis of many technically important substances. It is used in the manufacture of antipyrine (see Ch. 60) and its derivatives and for the synthesis of a large number of dyes and indole compounds.

Asymmetric diarylhydrazines are prepared like the corresponding aliphatic compounds, by reduction of diarylnitrosamines:



They are of some importance as reagents for the carbonyl group. The *symmetrical* diarylhydrazines (e.g. $\text{C}_6\text{H}_5\text{NH}\cdot\text{NHC}_6\text{H}_5$) are of greater interest. They are described in Chapter 34 under the name of *hydrazo-compounds*.

Oxidation of diazonium salts in alkaline solution (i.e. oxidation of the diazotates) by means of hydrogen peroxide gives nitranilides and nitrosophenylhydroxylamine compounds. The reaction is of interest since it shows that oxidation takes place partly at one and partly at the other nitrogen atom of the diazotate molecule. The reactions may obviously be formulated as follows:



CHAPTER 33

AZO-COMPOUNDS. AZO-DYES ¹

The term "azo-compounds" comprises those compounds which contain the group $-\text{N}=\text{N}-$ (linked to organic radicals). The simplest aromatic azo-compound is *azobenzene*, $\text{C}_6\text{H}_5\text{N}=\text{NC}_6\text{H}_5$.

Azo-compounds can be prepared in various ways:

1. By alkaline reduction of nitro-compounds (see p. 451). Iron or zinc dust and alkali, sodium amalgam and dilute alcohol, or alkaline stannous hydroxide solution can be used as reducing agents:

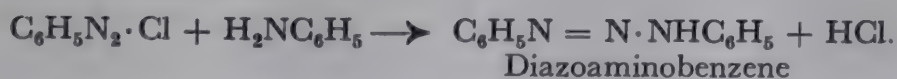


2. By boiling equimolecular amounts of aromatic primary amines with nitroso-compounds in glacial acetic acid (less often in alcohol) condensation takes place to azo-compounds, with elimination of water:



3. The most important method, and the one solely used technically is the *coupling of diazonium salts* with primary, secondary, and tertiary amines, phenols, and phenolic ethers. Even some unsaturated aliphatic and aromatic hydrocarbons are capable of coupling.

Diazonium salts first react with primary and secondary aromatic amines to give diazoamino-compounds:

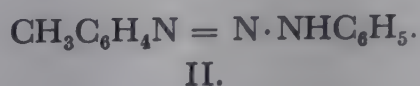
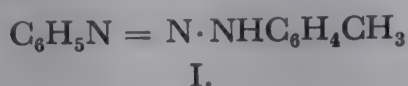


¹ See J. C. CAIN, *The Chemistry and Technology of the Diazo-Compounds*, New York, (1920). — H. E. FIERZ-DAVID, *Künstliche organische Farbstoffe*, Berlin, (1926). — ALBERT BRUNNER, *Analyse der Azofarbstoffe*, Berlin, (1929). — J. F. THORPE and R. P. LINSTEAD, *The synthetic dyestuffs and the intermediate products from which they are derived*, London, (1933). — FRITZ MAYER, *Chemie der organischen Farbstoffe*, 3rd ed., Berlin, (1934). — GUSTAV SCHULTZ, *Farbstoffe*, 7th ed., (1931); 1st and 2nd supplements, Berlin, (1934 and 1939). — K. H. SAUNDERS, *The aromatic diazo compounds and their technical applications*, London, (1936). — H. E. FIERZ-DAVID, *Künstliche organische Farbstoffe, Ergänzungsband*, Berlin, (1935 and 1938). — H. E. FIERZ-DAVID und L. BLANGEY, *Grundlegende Operationen der Farbenchemie*, 4th ed. (1938). — E. KNECHT, C. RAWSON and R. LOEWENTHAL, *A Manual of Dyeing*, 2 vols., 9th ed., London, (1941). — FRITZ MAYER, *The Chemistry of Natural Coloring Matters*, translated and revised by A. H. Cook, New York, (1943).

These are also formed when nitrous acid acts upon aniline bases; for this reason they are produced during diazotization if insufficient mineral acid is present (see p. 472).

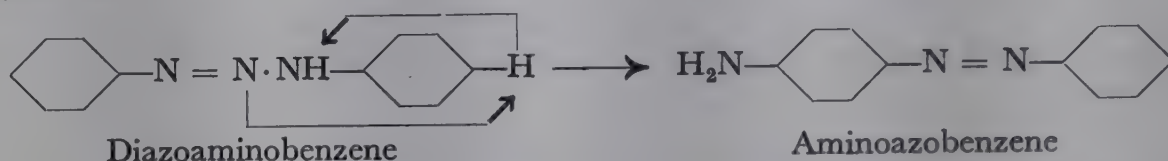
The diazoamino-compounds are yellow, and crystallize well. They have weak basic properties, combining with acids, and, on the other hand, they can form salts with metals (Cu, Ag, K) by replacement of the hydrogen atom attached to the nitrogen.

This hydrogen atom is mobile and can migrate from one nitrogen atom to another. This follows from the experiment: if a phenyldiazonium salt is coupled with toluidine, and if a tolyldiazonium salt is coupled with aniline, the two products are identical, whilst in the first case a compound of formula I would be expected to be produced, and in the second a compound of formula II:

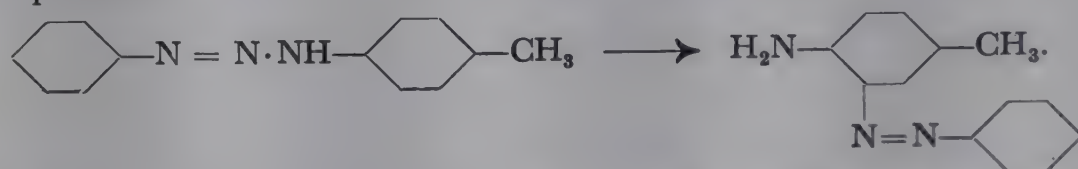


More accurate investigations of the constitution of this diazoamino-derivative make it probable that it has formula I, and that the more positive organic group (the toluene radical) is attached to the imino-group.

The most important property of the diazoamino-compounds is their rearrangement into aminoazo-compounds, which occurs on heating with the hydrochlorides of bases (e.g. aniline hydrochloride), or on treatment with excess mineral acid:

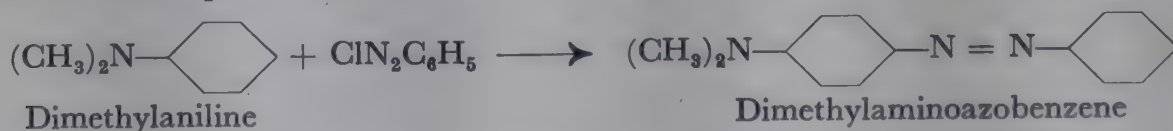


The rearrangement takes place to the *p*-position, but if this is occupied, to the *o*-position:

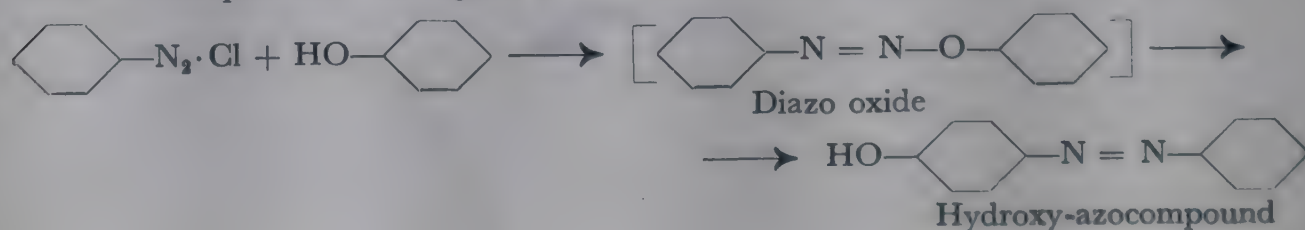


By these reactions aminoazo-dyes are made readily and in almost inexhaustible number.

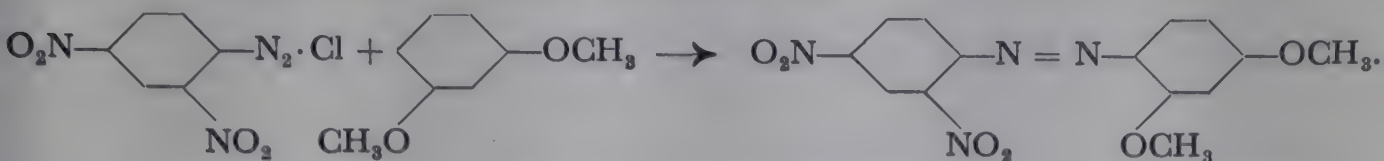
Tertiary aromatic amines couple with diazonium salts just as readily. Aminoazo-compounds are formed directly, the azo-group entering in the *p*-position with respect to the tertiary amino-group:



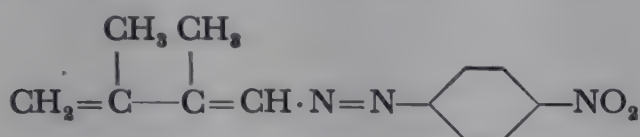
Diazonium salts react with phenols in alkaline solution to give hydroxyazo-compounds, and occasionally, but not always, *diazo oxides* are formed as intermediate compounds, analogous to the diazoamino-compounds (Dimroth):



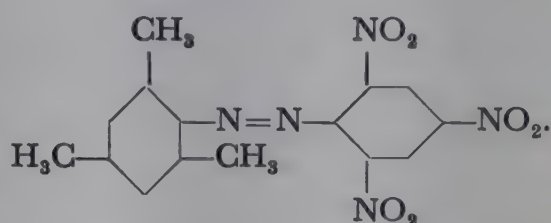
Also, phenolic ethers, which were formerly supposed to be incapable of entering into coupling reactions, may be converted into azo-dyes by combination with diazonium salts (Kurt H. Meyer). Their capacity for coupling is, however, smaller than that of amines and phenols. It is necessary to carry out the reaction in anhydrous solvents (the most convenient is glacial acetic acid). The ethers of *meta*-di- and trihydroxybenzenes react most easily:



Finally, also unsaturated hydrocarbons of the butadiene series, and even, in a special case, mesitylene, can combine with diazonium salts. The simplest diazonium compounds, however, do not react; diazonium compounds derived from the *nitrated* anilines, must be used, these compounds possessing particularly strong coupling power. Mesitylene will only couple with the diazonium salt of picramide (see p. 464) giving an azo-dye:

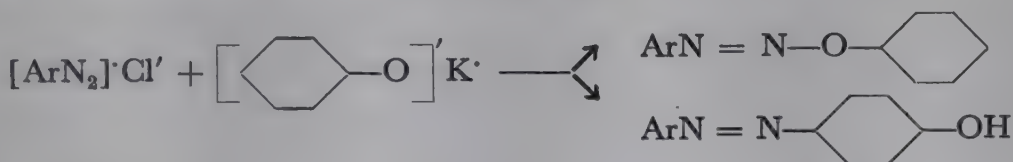


Azo-dye from dimethylbutadiene and diazotized *p*-nitraniline



Azo-dye from mesitylene and diazotized picramide

Dilthey distinguishes two possible *mechanisms* for coupling reactions. The reaction can begin with an ionic interchange, in which the primary attack of the diazonium salt takes place at the oxygen (or nitrogen) or at one of the carbon atoms:



Possibly both reactions go on together.

The second type of reaction consists in a direct addition of the diazonium salt to double bonds of the benzene nucleus, or to auxochromes (see p. 485) of the amine or phenol, the auxochrome first activating the unsaturated system.

The kind, and method of coupling in the case of naphthols and naphthylamines must be specially considered. α -Naphthol couples in the *p*-position to the hydroxyl, and if this is occupied in the *ortho*. In the case of β -naphthol the azo-radical takes up the 1-(α)-position. Naphthylamines, as a rule, behave in an analogous way. Exceptions are known, e.g. 1:5-naphthylenediamine. In the aminohydroxy-naphthalenes the hydroxyl group is the directing group in alkaline solution, and the amino-group in acid solution, so that it is possible to prepare different azo-dyes from the same aminonaphthol, according as the coupling is carried out in alkaline or acid solution.

The determination of the constitution of the azo-compounds is always carried out by reducing them to amines (e.g. with sodium hydrosulphite, or stannous chloride and hydrochloric acid). The mixture of monoamines, diamines, and hydroxy-amines thus obtained is then systematically separated into its compo-

nents. To detect their nature, spectroscopic methods are now also successfully used.

For example, reduction of aminoazobenzene gives a mixture of aniline and *p*-phenylenediamine:



Theory requires that azo-compounds should exist in *cis-trans* isomeric forms:



This isomerism has not yet been fully investigated. However, a *cis*-form of azobenzene has been obtained by the action of light on the stable *trans*-form. The *cis*-form has a different refractive index and absorption coefficient from the *trans*-form. On exposure to light an equilibrium is set up, the mixture containing about 27% *cis*- and 73% *trans*-form (G. S. Hartley).

Colour and dyes.¹ Before we consider a number of important azo-dyes, a general account of colour and dyes will be given.

It is an experimental fact that selective light absorption by a compound is always bound up with a certain degree of unsaturation of the compound concerned.

Thus, all substances whose molecules contain double or triple bonds ($\text{C}=\text{O}$, $\text{C} \begin{smallmatrix} \nearrow \text{O} \\ \searrow \text{OH} \end{smallmatrix}$,

$\text{N}=\text{O}$, $\text{N} \begin{smallmatrix} \nearrow \text{O} \\ \searrow \text{O} \end{smallmatrix}$, $\text{N}=\text{N}$, $\text{C}=\text{C}$, $\text{C}\equiv\text{C}$, $\text{C}=\text{S}$, etc.) have the capacity of absorbing light of certain wavelengths. The compounds showing this selective absorption are called, in the wider sense, "coloured".

Very many of these substances, however, absorb only light of wavelengths lying in the ultra-violet or infra-red. To the eye they therefore appear colourless. Substances are called "coloured" in the usual sense (yellow, red, blue) when they absorb light in the visible part of the spectrum.

Atoms, or groups of atoms, which are thought to be responsible for light absorption, and therefore for colour, are called *chromophores* (chromophoric groups) according to a suggestion due to O. N. Witt. It is an experimental fact, that usually such groups are "unsaturated", as mentioned above. (For example, the azo-dyes contain the chromophore $-\text{N}=\text{N}-$).

Unsaturation in molecules can be caused by single atoms which are in a coordinately unsaturated state. Dilthey and Wizinger define "chromophores" in this sense as coordinately unsaturated atoms. The above-mentioned "chromophoric groups" always contain such coordinately unsaturated atoms in consequence of their double or triple bonds. There is a considerable increase in the light absorption, according to Dilthey, when there is a transition from the coordinately unsaturated state to the ionic state. The intense colour of the carbonium salts (triphenylmethane dyes, etc.) can be explained in this way (cf. p. 608).

The modern atomic theory which traces the properties of matter to the

¹ See the text-books on dyestuff chemistry (p. 481, footnote), also: H. KAUFFMANN, *Die Auxochrome*, Stuttgart, (1907). — J. K. WOOD, *Chemistry of Dyeing*, London, (1926). — R. WIZINGER, *Organische Farbstoffe*, Berlin and Bonn, (1933).

structure of the atomic nucleus and the number and arrangement of the electrons, bases the conception of chromophores on a special, unstable arrangement of the electrons. Chromophores are thus atoms the electrons of which take up more energy-rich quantum states by the absorption of radiation. This definition leads to the conclusion that, in principle, each atom and ion, with the exception of the H-ion, can possess chromophoric properties, since they all contain valency electrons, which can take up higher quantum states. Actually, even saturated hydrocarbons show selective absorption, though only in the far (short-wave) ultra-violet.

Distorted arrangements of electrons are evidently present to a specially high degree in radicals and ions, in which electrons are missing, the total number not agreeing with the nuclear charge. The colour of triphenylmethyl, and other radicals as well as that of the carbonium salts (triphenylmethane dyes, etc., cf. p. 608) can be explained in this way.

Colour is in the highest degree a constitutive property. Compounds with the same composition but of different structure or configuration may possess totally different colours. Attempts have often been made to establish some law connecting colour and chemical constitution, but with relatively little success. Only within small groups of closely related compounds has it been possible, occasionally, to discover more or less valid relationships.

If, when a substance undergoes any chemical change, e.g. by substitution, its colour changes from yellow towards the red and violet (the absorption of the compound thus changing from violet to green and yellow), i.e. towards shorter wavelengths, the colour is said to *deepen*, the reverse case being a *lightening* of the colour. Substituents causing a deepening of colour are called "*bathochromic*" groups, and those which produce the opposite effect are called "*hypsochromic*" groups.

In addition to the chromophores, the *auxochromes* are of great importance in connection with dyes. These are salt-forming groups (NH_2 , OH, SO_3H , COOH , etc.) which intensify the colour of the compound. They must usually be present if a coloured substance is to act as a dye, i.e. to attach itself to the fabric to be coloured. Auxochromes can produce bathochromic or hypsochromic effects. If the dye has an acidic nature owing to the presence of carboxyl, sulphonic acid, or hydroxyl groups, it is referred to as an *acidic dye*, whereas if it has a basic nature, it is called a *basic dye*.

Organic dyes are mainly used to colour textiles. These can be classified under three main groups, according to their nature and chemical composition:

(a) vegetable fibres, amongst which are cotton, hemp, jute, and flax. They all consist of more or less pure cellulose, and are approximately neutral in character.

(b) artificial silk threads, which are produced by various methods from cellulose (see p. 367–8). With the exception of acetate rayon they are made up of regenerated cellulose, and possess in general the same characteristics as the latter. The process of manufacture often introduces slight chemical decomposition (oxidation, hydrolysis) of the material.

(c) animal fibres. The most important of these are wool and silk. They consist of proteins, and are therefore amphoteric in nature, i.e. they are capable of combining with both acids and bases.

The choice of dye and the method of dyeing are governed by the nature of the textile fibre. Not all fabrics require the same treatment. The most readily dyed are wool and silk. Most acidic and basic dyes attach themselves more or less strongly to them. The vegetable fibres, particularly cotton, and the various kinds of artificial silk, on the other hand, can only be dyed by definite groups of colloidal dyes, which are called *substantive* or *direct dyes*. It is possible, however, to make them take up other dyes if they are *mordanted*.

Metallic, or *basic mordants*, and *acidic mordants* are recognized. In the case of the first, the fabric is steeped in a solution of a readily hydrolysed metal salt. Usually aluminium, ferric, or chromium acetates or alums, or stannic salts are used. After this the yarn is steamed, i.e. placed in superheated steam, which causes the salt to hydrolyse, and to deposit the colloidal basic salts. These are fixed in a finely divided form on the fibre as they are produced. This mordanted yarn is now put into a solution of a dye which can combine with the metal salt to produce a complex compound. A "lake" is thus formed which remains attached to the fibres by means of the metal salt. The dye is thus fixed; it is said to be "fast".

For the acid mordanting of cotton, tannic acid is usually employed. It is adsorbed by the fibre, and reacts with basic dyes, being an acid, thus fixing them on the cotton.

A good deal of experimental material in connection with the mechanism of the process of dyeing has accumulated, but although the matter has been discussed with considerable zeal the question has not been completely solved. In certain cases, Witt's solution theory appears to be correct. According to this the dye forms a solution with the fibre and distributes itself according to Henry's Law between it and the water, as between two immiscible liquids. Certain dyes are attached in this way, for example, by acetate rayon and nitro-cellulose (Kartaschoff, K. H. Meyer). This process may also be of importance in connection with the dyeing of wool and silk by *basic* dyes.

In other cases, adsorption of the dye by the yarn seems to take place. Georgievics has shown that the attachment of many substantive dyes to cotton is governed by the adsorption isotherm. The processes in the case of wool and silk dyeing are the most debated. Whilst many workers regard these processes also as pure adsorption, many others, like Chevreul, regard them as salt formation between dye and fibre. Since wool and silk are amphoteric in nature, it can be readily understood that they can combine with the acidic or basic groups of the dye forming salts.

More recently the attachment of organic acids and acidic dyes to wool and silk has been very thoroughly investigated by K. H. Meyer. This work showed that acidic dyes are fixed by the two types of fibre in the ratio of their equivalent weights, completely independently of the chemical nature of the dye; 1200 g of wool combine with one equivalent of acid. The animal fibre thus behaves as a base with respect to acidic dyes. These dyeing processes must therefore be regarded as simple processes of salt formation.

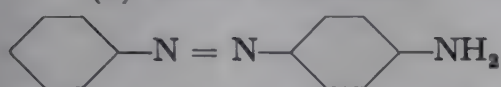
The view that dyeing is the result of chemical combination of the dye with the animal fibre can be supported by other interesting experiments. The dye fuchsin (see p. 613) forms a colourless base, from which acids regenerate the red salt. If silk is put into the *colourless* solution of the fuchsin base, it is coloured red.

It thus appears that acidic groups of the silk have formed salts with the fuchsin base. A second, similar experiment is as follows: the yellow ethyl ester of tetrabromophenolphthalein (see p. 610) gives blue alkali-metal salts. Silk becomes *blue* when placed in the *yellow* solution of the compound. The simplest explanation of this phenomenon is that the basic amino-groups of the silk react with the ethyl ester of tetrabromophenolphthalein forming salts. Finally, it must be mentioned that cotton, into which amino-groups have been introduced chemically, reacts readily with acids, but shows no affinity for bases. It would be difficult to explain this in any other way than by supposing that there is salt formation between the treated yarn and acidic dyes.

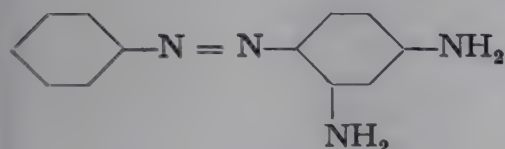
The difference between the "adsorption theory" and the "theory of salt formation" has become much less well defined since adsorption has come to be regarded as a process in which the valency forces of the atomic lattice of the adsorbent are responsible for adsorption, as these valency forces are identical with normal chemical valencies. The fixing of dyes on wool and silk, therefore, doubtless takes place by these free lattice valencies, and since these are electrostatic in nature (positive and negative), the affinity for acidic and basic dyes can readily be understood.

Individual Azo-dyes

(a) BASIC AZO-DYES.

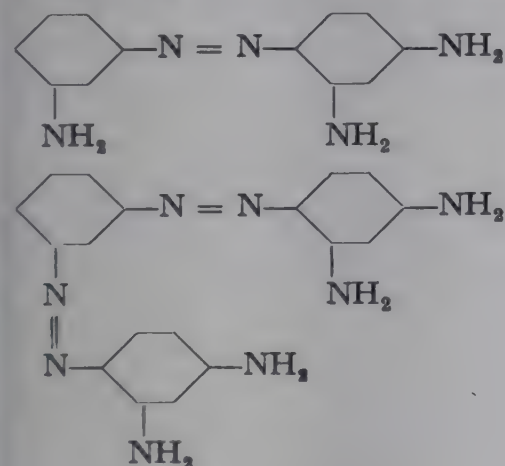


p-AMINOAZOBENZENE, ANILINE YELLOW, dyes yellow. The colour, however, is very sensitive to acids (turning violet). It serves as a starting point for making other dyes.

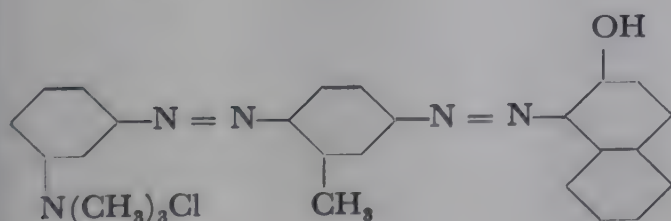


CHRYSOIDINE (prepared from diazotized aniline and *m*-phenylenediamine), dyes cotton mordanted with tannin a brownish red. If the group $\text{—SO}_2\text{NH}_2$ is introduced in the *p'*-position in the chrysoidine molecule, a

compound is obtained of which the hydrochloride is used under the name *Prontosil* (rubrum) in the treatment of streptococcal infections.



BISMARCK BROWN. A mixture of these two azo-dyes is produced by the action of nitrous acid on *m*-phenylenediamine (the technical product contains homologues in addition). Bismarck brown is used for dyeing leather and for the synthesis of poly-azo-dyes.



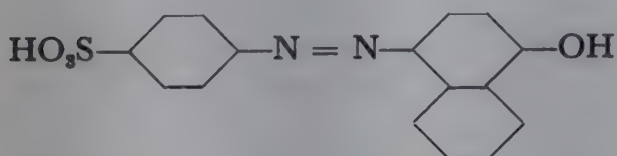
JANUS RED is prepared by diazotizing *m*-aminophenyl-trimethylammonium chloride, coupling with *m*-toluidine, then diazotizing the mono-azo-dye and coupling with β -naphthol. Janus red, and the com-

pounds related to it, have the property of dyeing cotton and wool from an acid bath approximately the same colour, and are therefore used for dyeing cotton-wool mixtures, and also artificial silk.

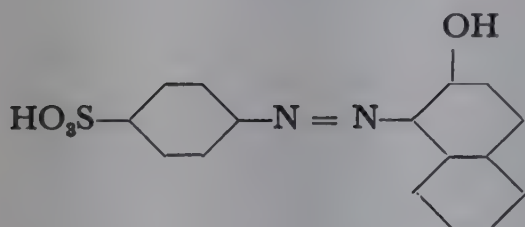
(b) ACIDIC AZO-DYES.

OS(=O)c1ccc(cc1)/N=N/c2ccc(cc2)N(C)C **METHYL ORANGE**, helianthine, or **Orange III**, is not used as a dye, but owing to its sensitivity to acids it is used as an indicator in acidimetry. It is prepared by coupling diazotized sulphanilic acid with dimethylaniline.

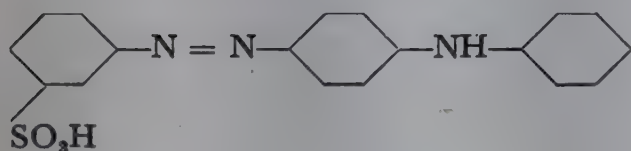
FAST YELLOW G, the *m,p'*-disulphonic acid of *p*-aminoazobenzene, is formed by the sulphonation of the latter.



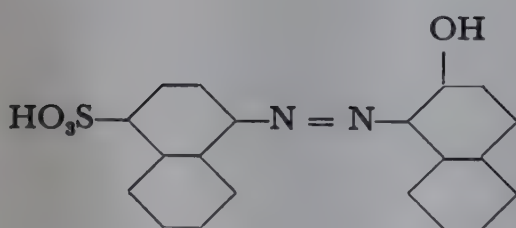
α -NAPHTHOL ORANGE, or **Orange I**, prepared by coupling diazotized sulphanilic acid with α -naphthol, dyes wool and silk, but is not so much used as



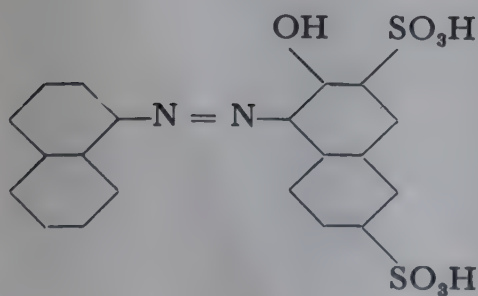
β -NAPHTHOL ORANGE, or **Orange II**, one of the most commonly used acidic dyes.



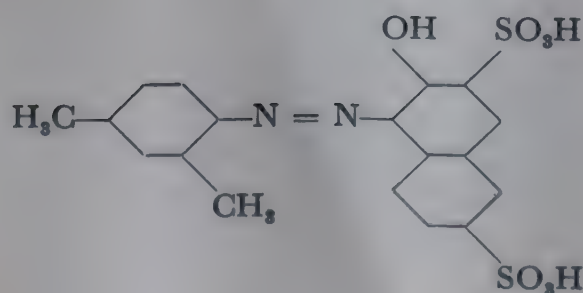
METANIL YELLOW, is made from diazotized metanilic acid and diphenylamine.



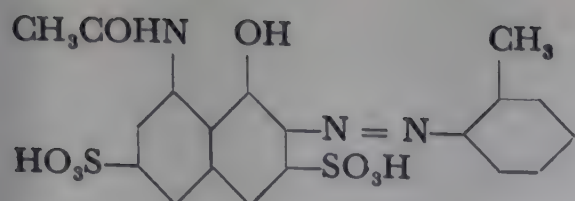
FAST RED A, made from diazotized naphthionic acid and β -naphthol, is the cheapest red acidic dye. It is fairly difficultly soluble, and is fast to washing. The replacement of sulphanilic acid (in Orange II) by naphthylaminesulphonic acids deepens the colour.



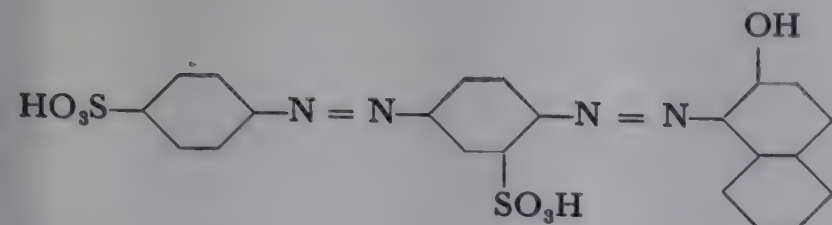
FAST RED B, or **BORDEAUX B** is prepared from α -naphthylamine and R-acid. It dyes a bluish red colour.



PONCEAU 2 R is made from diazotized *m*-xylydine and R-acid. The Ponceau colours are brilliant scarlet-red, and are used as substitutes for cochineal (see p. 598) though they do not approach it in fastness to light. Ponceau 2 R finds extensive use.

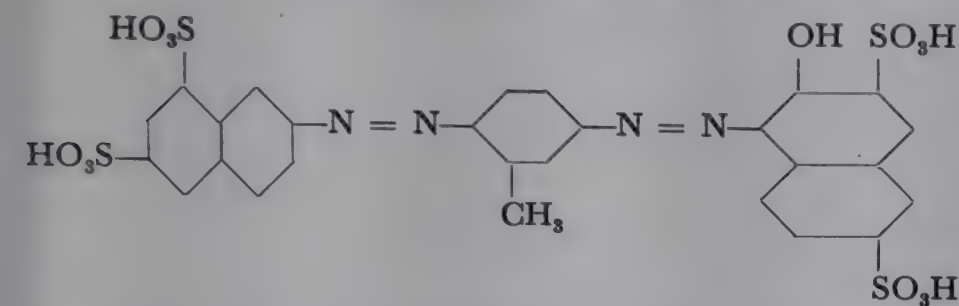


SUPRAMINE REDS. These are red dyes which contain a N-acyl group, either in the diazotized component or in the coupled component. For example, SUPRAMINE RED 3 B is the azo-dye from *o*-toluidine and N-acetyl-H-acid.



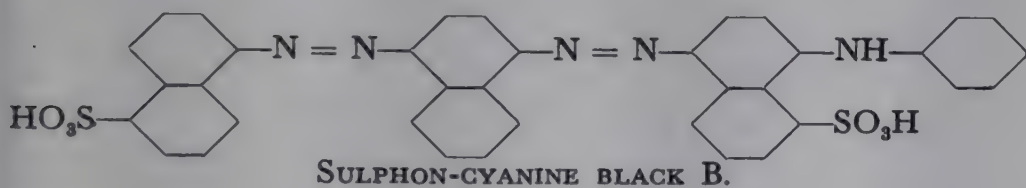
BIEBRICH SCARLET, is prepared by diazotizing Fast yellow, and coupling it with β -naphthol. It dyes wool scarlet-red.

CROCEINE SCARLET 3 B is made by coupling diazotized aminoazobenzene-sulphonic acid with β -naphthol-8-sulphonic acid. It dyes wool red.

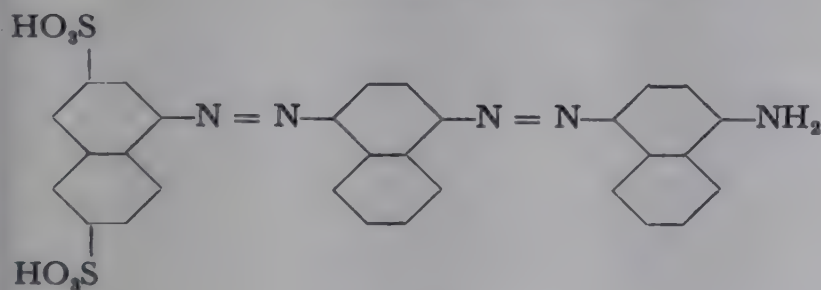


BRILLIANT CROCEINE 9 B

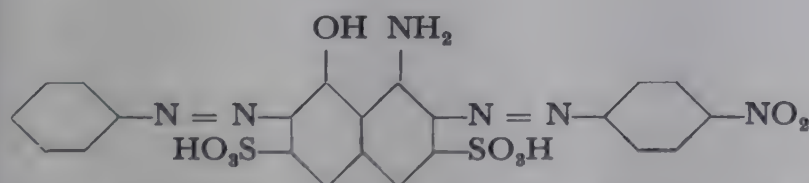
BRILLIANT CROCEINE 9 B is made from diazotized amino-G-acid, which is coupled with *m*-toluidine, the mono-azo-dye being re-diazotized and coupled with R-acid. The dye is still red. If, however, the tolyl radical is replaced by the naphthalene group, the colour deepens strongly towards black-violet.



SULPHON-CYANINE BLACK B.

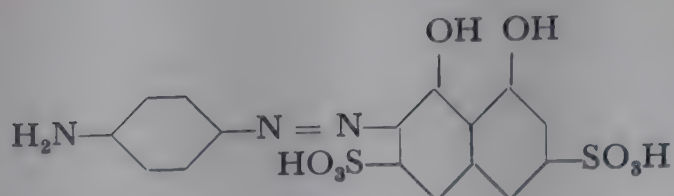


NAPHTHYLAMINE BLACK D.



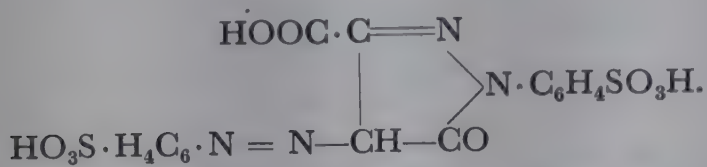
NAPHTHOL BLUE-BLACK B, is prepared by coupling H-acid with diazotized *p*-nitraniline in acid solution, and then

with diazotized aniline in alkaline solution. It has considerable industrial use, especially when mixed with Naphthylamine black D. This mixture is known as Acid black 4 B. It is used as a wool dye and a substitute for logwood.

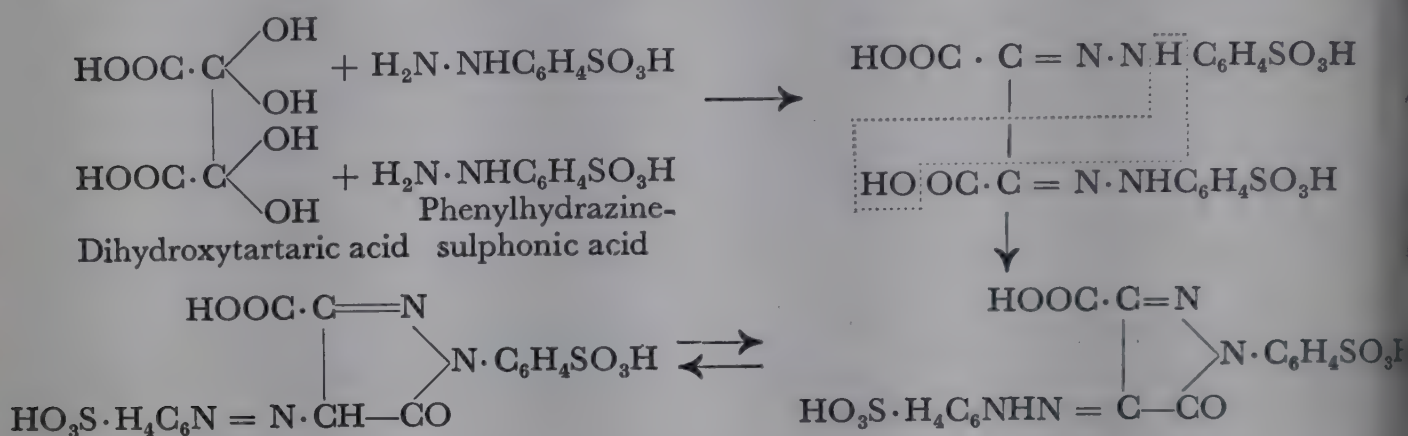


VICTORIA VIOLET 4 BS, is made from *p*-phenylenediamine and chromotrope acid. The azo-dyes which have chromotropic acid as a component (e.g. Chromotrope 2 R,

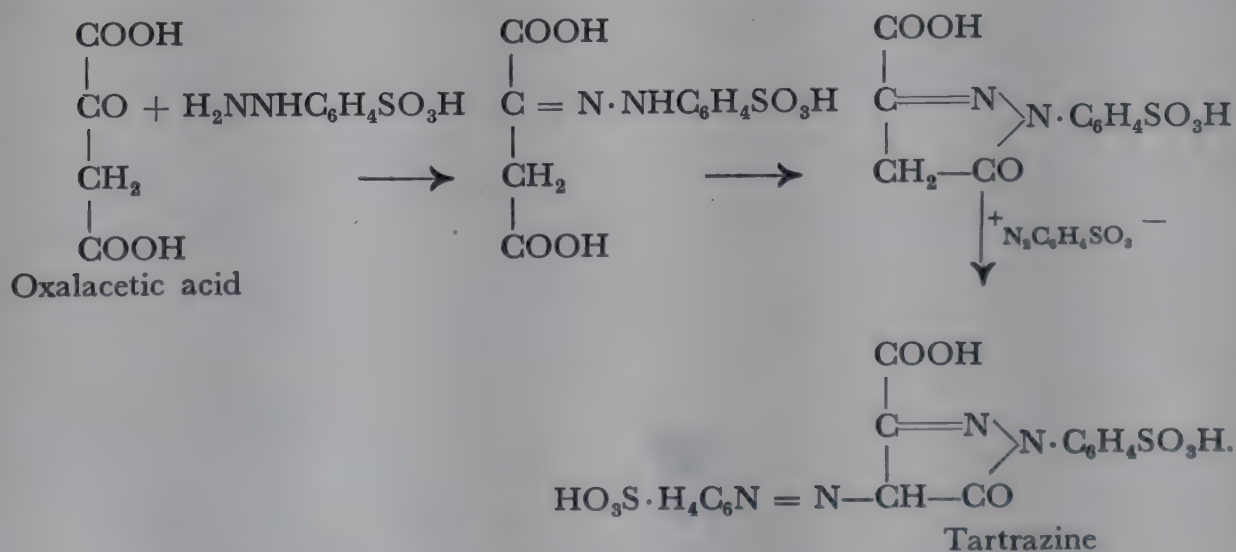
Victoria violet 4 BS, and many others) colour wool bluish red to violet from an acid bath. If these colours are then treated with a solution of potassium dichromate the colour deepens towards blue to black. Such dyes are known as chrome dyes (see later).



dye to be discovered (Ziegler, 1884). It was made by acting on phenylhydrazine-sulphonic acid with dihydroxytartaric acid:



It is now usually obtained technically by condensing oxalacetic ester and phenylhydrazinesulphonic acid giving sulphophenylpyrazolonecarboxylic acid, and this is coupled with diazotized sulphanilic acid:

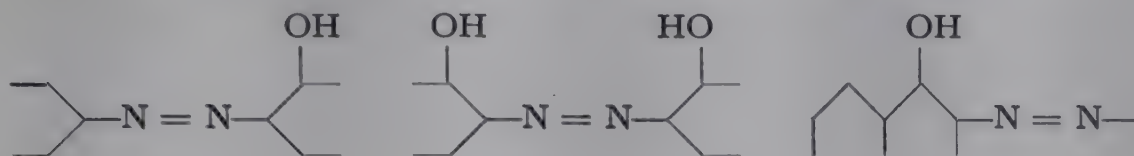


The pure yellow colour and good fastness to light of tartrazine has led to the synthesis of many homologous and analogous compounds. The group of pyrazolone dyes is therefore a large one.

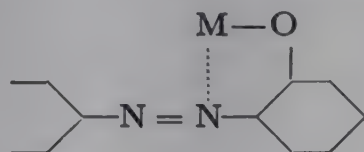
(c) MORDANT DYES AND CHROME DYES.

In order that a dye should be fixed by a metallic mordant it must possess the power of combining with the metal salts to form internal complex compounds or "lakes". Substances which tend to form internal complex salts have already been met with in different parts of this book. For example, we may recall the enol form of acetoacetic ester and similar substances, the aliphatic α -amino-acids, *ortho*-dihydroxybenzenes, *o*-hydroxycarboxylic acids (e.g. salicylic acid) and others. Similar groupings must also be present in the molecules of the azo-dyes if these are to possess the power of combining with mordants.

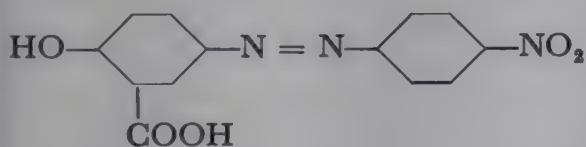
The most important mordant dyes contain the salicylic acid (or methyl-salicylic acid = *o*-cresotic acid) radical, or they are derived from *o*-aminophenols or *o*-aminonaphthols, and thus contain groupings such as:



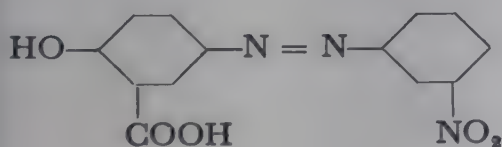
which tend to form internal metallic complex salts of the type:



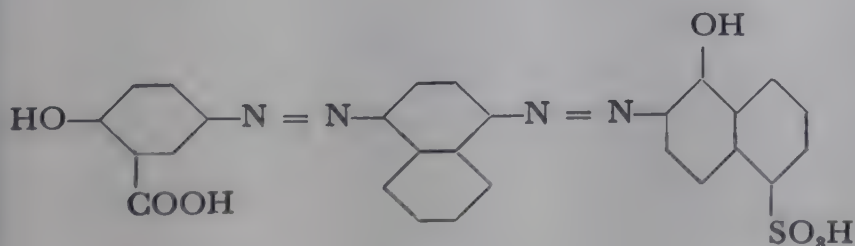
The azo-dyes derived from the *o*-aminophenols also have the peculiarity of changing their shades on after-treatment of the dyed wool with potassium dichromate. The colour is usually deepened considerably. This process is called "*chroming*". The colours produced in this way are very fast. The primary process probably consists mostly in the partial oxidation of the dye by the dichromate. The latter is thus reduced to $\text{Cr}(\text{OH})_3$ which forms a lake with the oxidized dye. Cases are also known, however, where the chroming process occurs without oxidation of the dye, and the reaction leads to the formation of the chrome lake of the unchanged dye.



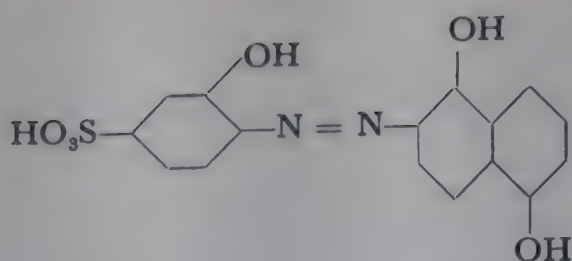
ALIZARIN YELLOW R. Yellow mordant dye.



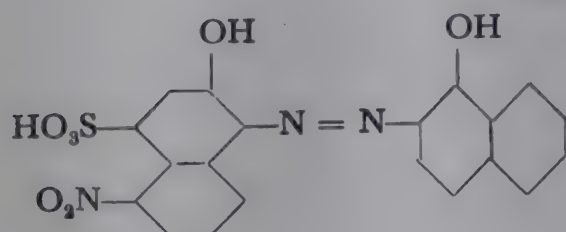
ALIZARIN YELLOW GGW. Important yellow mordant dye for calico printing.



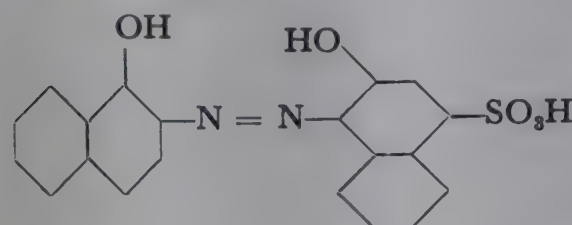
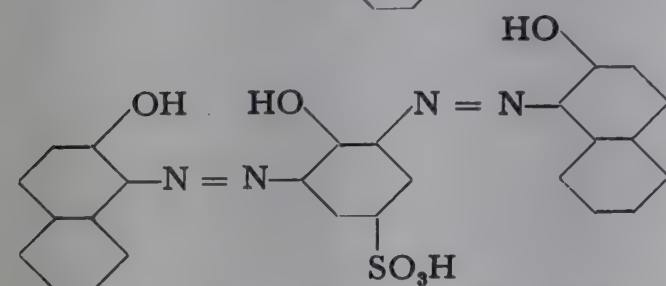
DIAMOND BLACK F. Mordant dye.



ERIOCHROME BLACK T.



DIAMOND BLACK PV. Blue-black colour; can be chromed.

ERIOCHROME BLUE-BLACK B.
Chrome dye.

ACID ALIZARIN BLACK SE.

It has recently been found possible to prepare the complex chromium and copper salts of dyes of this kind in the pure form. They are found in commerce under the names *neolan dyes* and *palatine fast dyes*. Rather surprisingly, they are readily soluble in water.

(d) DIRECT OR SUBSTANTIVE COTTON DYES.

Most of the azo-dyes mentioned above are not able to dye cotton directly. Until 1884 there was no synthetic dye which could colour cotton directly, and only a few of those occurring naturally, such as *safflower* (from the thistle *Carthamus tinctorius*), *Orleans* (from the fruit flesh of *Bixa orellana*), and turmeric, or curcuma (from the root of *Curcuma tinctoria*) possessed this valuable property.

In 1884 Böttiger discovered *Congo red*, which dyes cotton directly, and this was soon followed by many other products with similar properties. These compounds have no common, or analogous chemical structure, but experience has shown that the introduction of certain components usually brings about the desired effect. In particular, the following multinuclear diamines are used successfully as the starting materials for the synthesis of direct cotton dyes:



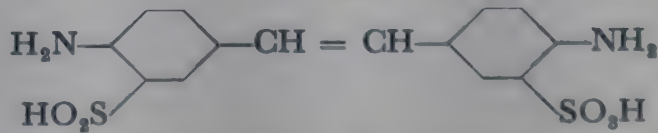
Benzidine



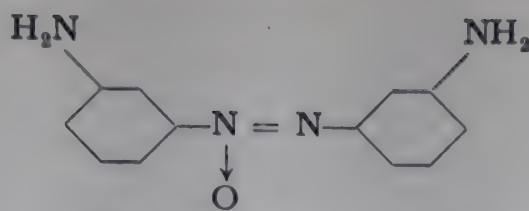
o-Tolidine



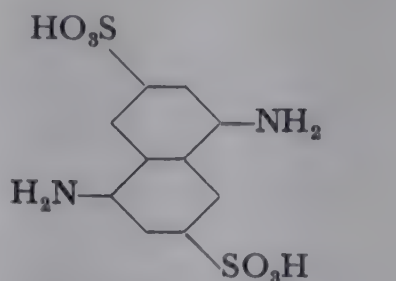
o-Dianisidine



Diaminostilbenedisulphonic acid

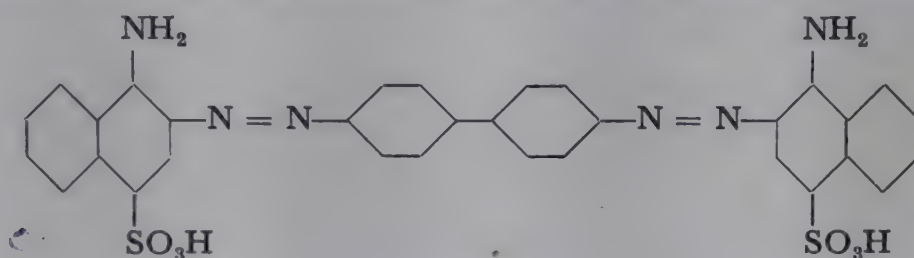


Diaminoazoxybenzene

*p*-Phenylenediamine1:5-Naphthylenediamine-
3:7-disulphonic acid

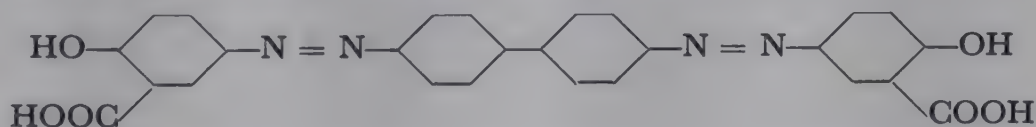
The dyeing of cotton by substantive dyes very probably depends on adsorption (see p. 486). These dyes all have a definite colloidal character. Salt is added during the dyeing ("Salzfarben"). This appears to favour the precipitation of the dye on the fibre, as with other colloids.

CONGO RED is prepared from bis-diazotized benzidine and naphthionic acid. The substance dyes red, but the colour is sensitive to acids, and is turned blue by mineral acids. Congo red is therefore used as an indicator for mineral acids.

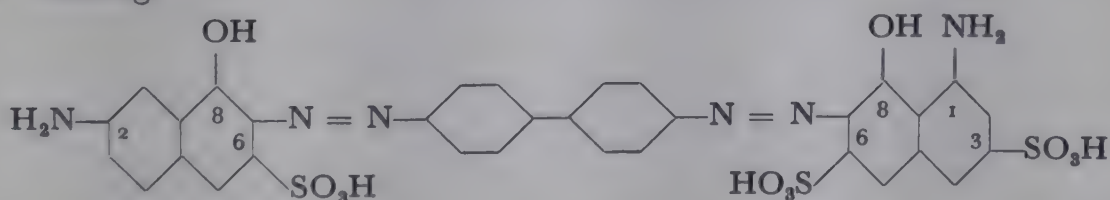


BENZOPURPURINE 4B is made from *o*-tolidine and naphthionic acid. It has similar dyeing properties to Congo red, but is somewhat less sensitive to acids. It is one of the most important red dyes for cotton.

CHRYSAMINE, prepared by bis-diazotizing benzidine and coupling with salicylic acid, is particularly used for calico printing.

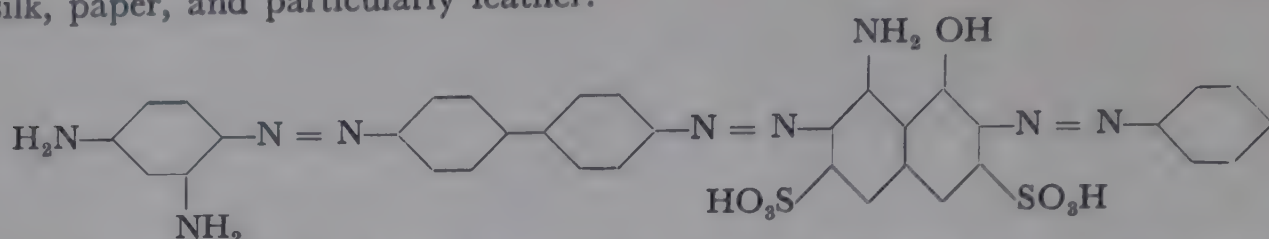


DIAMINE BLACK B.H. This product can be diazotized on the fabric and developed with *m*-phenylenediamine or β -naphthol to give a black dye, which is very fast to washing.

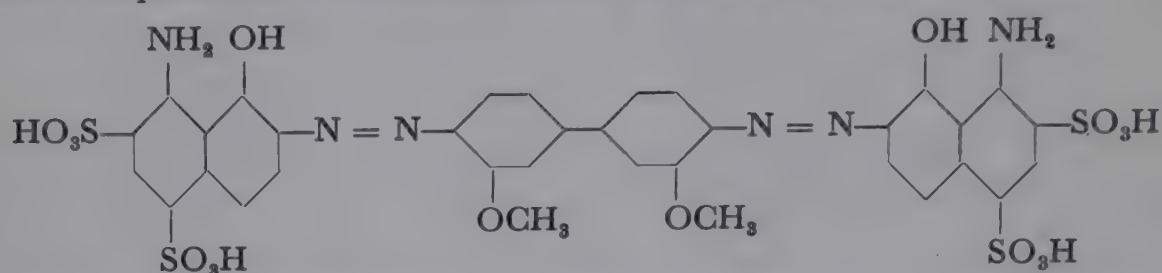


DIRECT DEEP BLACK. This is prepared by coupling bis-diazotized benzidine in acid solution on the one hand with H-acid, and on the other with *m*-phenylenediamine, and then acting on the bis-azo-dye thus formed with a phenyldiazonium

salt in alkaline solution. Direct Deep black is used to a large extent in dyeing wool, silk, paper, and particularly leather.

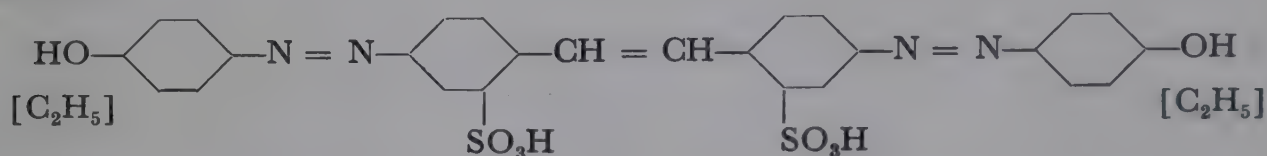


DIAMINE PURE BLUE FF, or CHICAGO BLUE, is obtained from dianisidine and 1-amino-8-naphthol-2:4-disulphonic acid. It dyes a pure blue shade.

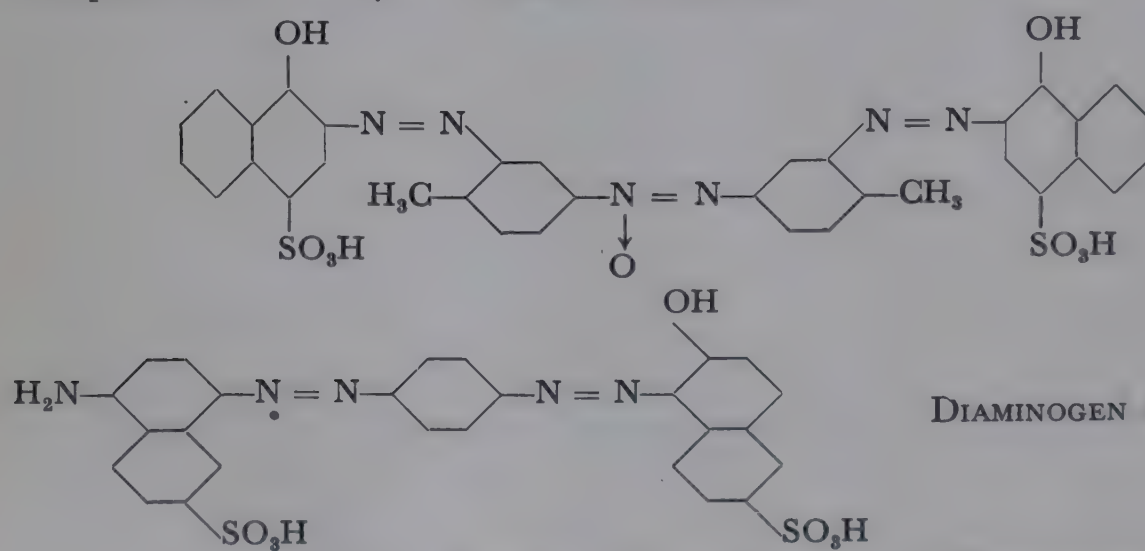


DIAMINE PURE BLUE is made from diazotized dianisidine and H-acid in alkaline solution.

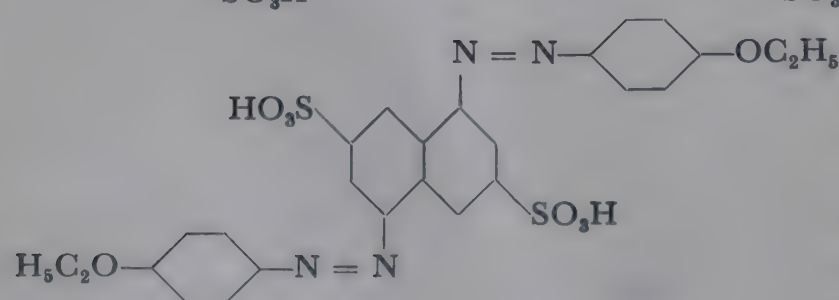
BRILLIANT YELLOW. This is made from 4-nitrotoluene-2-sulphonic acid via the diaminostilbenedisulphonic acid and phenol. It is used particularly for dyeing paper. Its sensitiveness towards alkalis is avoided by ethylation of the hydroxyl groups. In this way CHRYSOPHENINE, a very important yellow dye for cotton, is obtained.



ST. DENIS RED is made from diazotized diaminoazoxytoluene and α -naphthol-4-sulphonic acid. It dyes a bluish red, and is fast.



DIAMINOGEN BLUE BB.



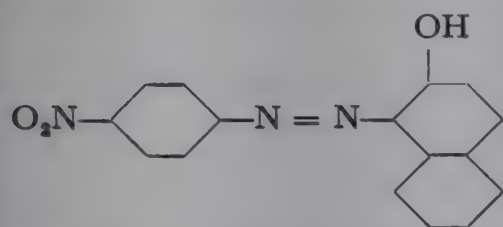
DIAMINE GOLDEN YELLOW, a good, fast, yellow, cotton dye is made from 1:5-naphthylenediamine-3:7-disulphonic acid and phenol, the product then being ethylated.

(e) AZO-DYES PRODUCED ON THE FIBRE. ICE COLOURS.

Since the fastness to washing of fabrics dyed with azo-dyes is greater according as the dye concerned is less soluble, attempts have been made to produce water-insoluble azo-dyes directly on the fibre. In the finely divided form in which they are thus obtained they are permanently fixed on the cotton, probably by adsorption.

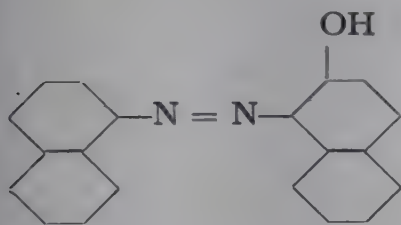
The dyeing process is carried out as follows. The cotton is impregnated with an alkaline solution of a phenol (usually β -naphthol). It is then wrung out and dried, and the fabric is then passed through a solution of a diazonium salt. Coupling takes place on the yarn giving (insoluble) dyes which in many cases are well retained by the fabric. Since the diazonium salt solution must, as a rule, be kept in ice, the dyes so produced have been called *ice colours*. 2-Hydroxy-3-naphthoic acid anilide ("Naphthol AS"), which is much used nowadays in place of β -naphthol, also remains attached to the undried fabric.

By coupling Naphthol AS on the fabric with various diazonium salts exceedingly important colour shades are produced, varying from yellow-red to blue. For example, with *m*-chloroaniline, a yellow-red colour is obtained, and with *p*-methoxy-*p'*-aminodiphenylamine a beautiful reddish blue, which matches indigo.



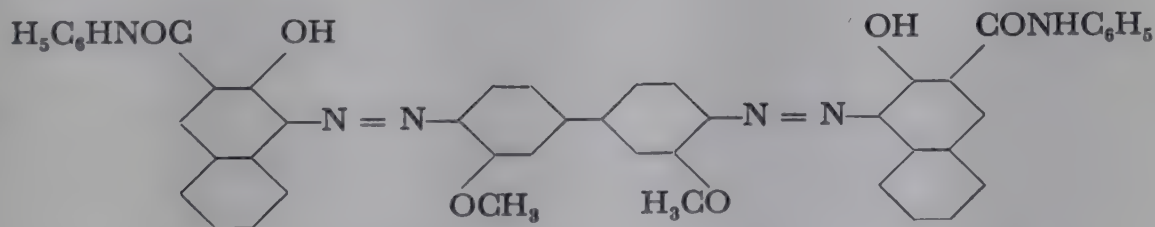
The first important compound of the ice colour type was NITRANILINE RED, prepared from diazotized *p*-nitraniline and cotton impregnated with β -naphthol.

Many similar substances succeeded it, such as PHENETIDINE RED (diazotized nitrophenetidine + β -naphthol).



NAPHTHYLAMINE BORDEAUX (diazotized α -naphthylamine + β -naphthol).

Azo-dyes from tetrazotized dianisidine + 2-hydroxy-3-naphthoic acid anilide (Naphthol AS)



To make the preparation of diazonium salt solutions which are necessary for the synthesis of ice colours easier, the stable *anti*-diazotate (see p. 475) of *p*-nitraniline has been put on the market under the name *Nitrosamine red*. The dyer need only dissolve this in water and acidify the solution with mineral acid in order to obtain a coupling solution of a diazonium salt. The *anti*-diazotates are converted into diazonium salts on adding excess mineral acid.

A method based on another principle provides stable, non-explosive diazonium salts by mixing diazonium salts with aluminium sulphate, alum, or metallic salts of aromatic sulphonic acids, etc. In this "diluted" form they have lost most of their instability. Acid and neutral salts of diazonium compounds with naphthalenedisulphonic acids and complex metallic salts, such as H_2TiF_6 , H_2SnF_6 , H_2SnCl_6 , etc. are also fairly stable.

Mixtures of nitrosamines or stabilized diazo-salts with Naphthol AS components are put on the market under the names rapidogen, rapid fast dyes, or rapid azo-dyes, and are used in colour printing.

Azoxy-compounds. $\text{RN} = \text{NR}^1$



As their name implies, the azoxy-compounds may be regarded as oxy-derivatives of the azo-compounds. They are accordingly formed by the oxidation of azo-compounds with hydrogen peroxide:



Conversely they can be readily reduced to azobenzene and its derivatives.

A convenient method of obtaining azoxybenzene is the alkaline reduction of nitrobenzene (see p. 451). It is here produced from nitrosobenzene and phenylhydroxylamine, the first stages of the reduction:

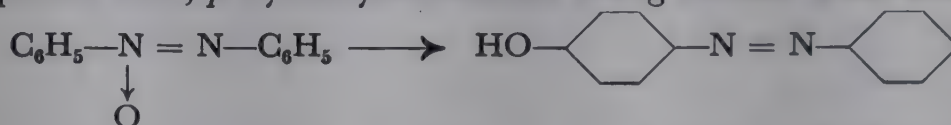


or from phenylhydroxylamine and unchanged nitrobenzene:



The simplest method of obtaining azoxybenzene is by boiling nitrobenzene with methanolic potash.

The azoxy-compounds are yellow, crystalline substances, almost insoluble in water. (Azoxybenzene melts at 36°). They isomerize under the influence of concentrated sulphuric acid, *p*-hydroxyazobenzene being formed from azoxybenzene:

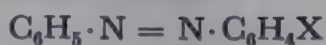


Exposure to light acts in a similar way, but leads to *o*-hydroxyazobenzene.

The constitution of the azoxy-compounds was for a long time disputed. In addition to the formulation used above, the following was also often used:



Angeli, however, discovered that monosubstitution products of azoxybenzene occur in two isomeric forms:

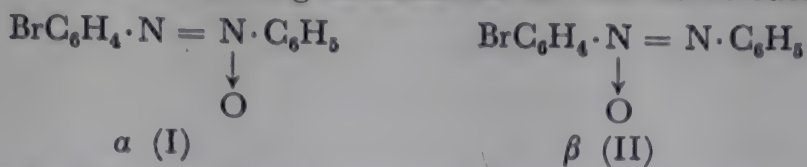


thus solving the question in favour of the unsymmetrical formula.

If, for example, monobromoazobenzene is oxidized with hydrogen peroxide, two isomeric azoxy-compounds, known as α - and β -forms, are produced. The first melts at 73° , the second at 92° . The α -form does not react with bromine, but

¹ See A. ANGELI, *Über die Konstitution der Azoxyverbindungen*. German translation by W. Roth. Stuttgart, (1913) (Sammlung Herz). — E. MÜLLER, *Die Azoxyverbindungen*, Stuttgart, (1936).

the β -isomeride readily takes up one atom of bromine by substitution. This led Angeli to put forward the following formulæ for the two isomerides:



Azobenzene itself is readily substituted by bromine. It is therefore, very probable that the easily brominated β -form of bromoazoxybenzene still has the grouping $=\text{N} \cdot \text{C}_6\text{H}_5$, and therefore has the formula II. In the α -form, on the other hand, the benzene nucleus attached to the trivalent nitrogen already contains a bromine atom, and is therefore unable to take up any more.

Another kind of isomerism has been observed with *o,o'*-azoxytoluene, *o,o'*-azoxyanisole, and similar compounds, which occur in two forms differing in their melting points and absorption spectra. They are possibly cases of *cis-trans* isomerism as shown by the formulæ (E. Müller):



CHAPTER 34

AROMATIC DERIVATIVES OF HYDRAZINE

The *monoarylhydrazines* and *asymmetrical diarylhydrazines* have already been considered in Chapter 32. In this chapter the *symmetrical diarylhydrazines* or *hydrazo-compounds*, and the *tetraarylhydrazines* will be described.

Hydrazo-compounds are formed by the reduction of nitro- and azo-compounds by means of zinc dust and alcoholic potash (see Chapter 31):



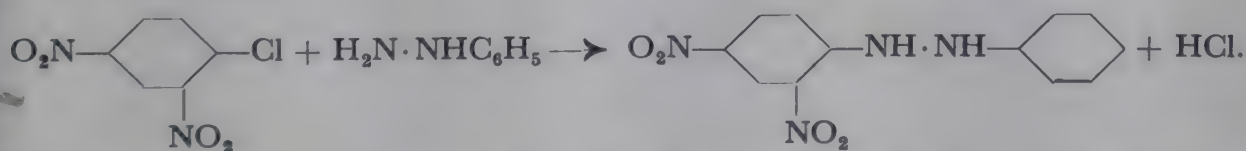
The quantity of reducing agent must be calculated from the amount of nitrobenzene used, since the hydrazo-compounds can be further reduced to amines. On the other hand, they are readily oxidized and are converted even by atmospheric oxygen or ferric chloride into azo-compounds.

Hydrazobenzene is a colourless, crystalline substance which melts at 126° . It is insoluble in water, but dissolves in many organic liquids. On heating in the dry state it disproportionates into aniline and azobenzene:



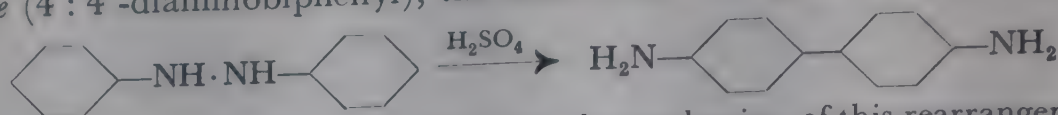
Part of the molecule is thus oxidized at the expense of the rest, which is reduced.

A good method of preparing several substituted hydrazo-compounds, especially nitrated ones, depends on the action of reactive aromatic halogen compounds on phenylhydrazine:



The most interesting and, from the practical point of view, most important property of the hydrazo-compounds is their ability to rearrange. Under the in-

fluence of concentrated mineral acids, hydrazobenzene is chiefly converted into *benzidine* (4 : 4'-diaminobiphenyl), the molecule, so to speak, turning inside out:

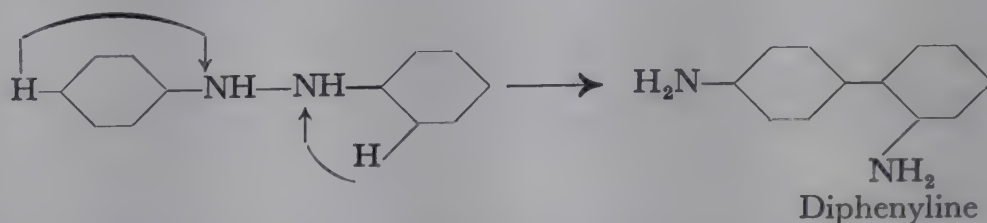


It may be pointed out in connection with the mechanism of this rearrangement that before the N—N link breaks completely, the 4,4'-positions must come within each other's sphere of influence; for if a mixture of two different hydrazo-compounds is made to undergo the rearrangement, only the symmetrical biphenyl derivatives are obtained. If dissociation of the RNH—radical takes place before the isomerization, biphenyl derivatives with differently substituted benzene rings would be expected to be produced according to the equation:

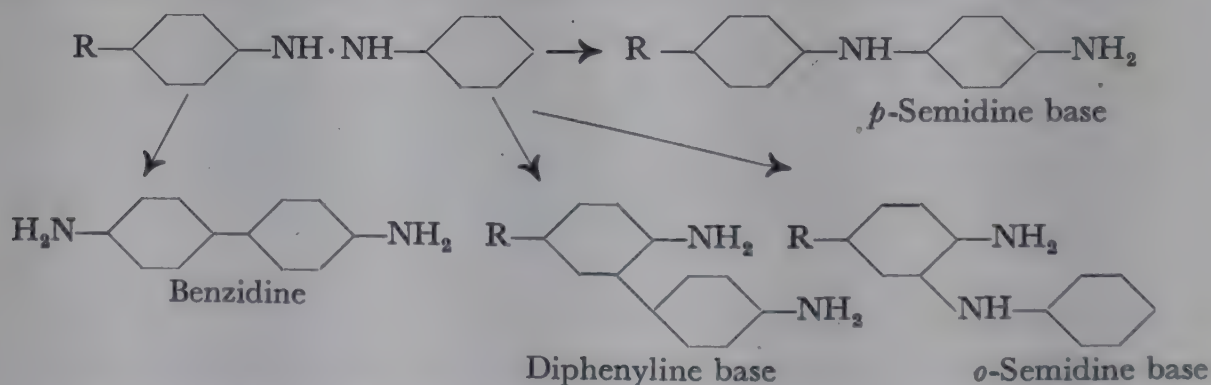


but these are not observed.

In addition to this, the principal reaction, known as the *benzidine rearrangement*, a subsidiary isomerization also occurs which gives 4 : 2'-diaminobiphenyl, or *diphenylene*. It is therefore known as the *diphenylene rearrangement*. In this case only one benzene nucleus reacts in the *para*-position to the amino-group, the other reacting in the *ortho*-position:



If a *para*-position in hydrazobenzene is already occupied by a substituent, there are still further possibilities of isomerization. In addition to a diphenylene base and a benzidine compound (the formation of the latter being accompanied by the elimination of the substituent), two diphenylamine derivatives are formed by "rotation" of only one of the benzene nuclei, the so-called *p-semidine* and *o-semidine* bases. These isomerizations are known as the *semidine rearrangement*:



The ratio in which the various isomerization products are formed varies a good deal, and depends chiefly on the nature of the substituent R.

The conversion of hydrazobenzene into benzidine is used practically for the preparation of benzidine. For this purpose it is not necessary to start with pure hydrazobenzene. Nitrobenzene can first be reduced in alkaline solution to the hydrazobenzene stage, and the product can be directly treated with acid. In another method, azobenzene is reduced in acid solution, benzidine being then formed in one operation. Benzidine gives a very difficultly soluble sulphate by means of which the base can be isolated.

Tetraarylhydrazines. These compounds are formed by the oxidation of diphenylamine and its derivatives:



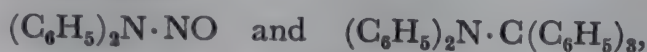
Tetraphenylhydrazine is a colourless compound which crystallizes well (m.p. 144°). It dissolves in concentrated sulphuric acid with a blue colour.

The tetraarylhydrazines are particularly interesting from the point of view of valency. Even the simplest compound of the whole series, tetraphenylhydrazine, dissociates on heating in toluene ($80-90^\circ$) to a small degree into diphenylamino radicals, $(\text{C}_6\text{H}_5)_2\text{N} \dots$



The process is thus analogous to the decomposition of hexaphenylethane into triphenylmethyl (p. 400).

In the case of tetraphenylhydrazine the equilibrium lies strongly in favour of the undissociated substance. The quantity of diphenylamino is small even at higher temperatures. It increases somewhat on diluting the solution. The free diphenylamino radicals unite at higher temperatures with other radicals, e.g. NO or $(\text{C}_6\text{H}_5)_3\text{C} \cdot$. The compounds

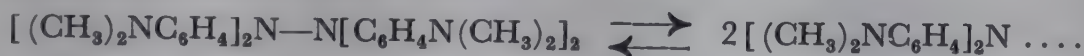


are thus formed quantitatively, because as the diphenylamino radicals are removed, more are formed by further dissociation of the tetraphenylhydrazine.

Like triphenylmethyl and its analogues, these unsaturated diarylamino radicals, with "divalent" nitrogen atoms, are *coloured*.

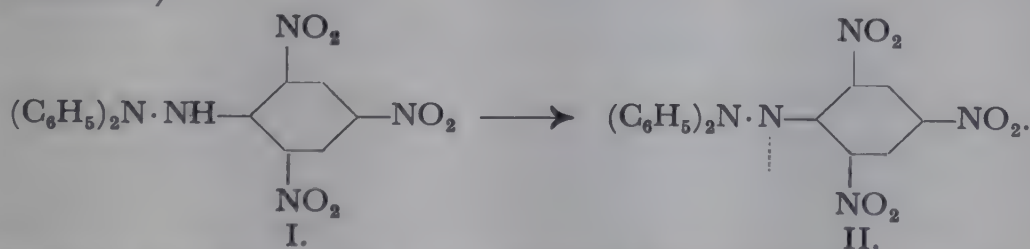
The systematic investigation of Wieland has shown that the tendency of the tetraarylhydrazines to dissociate increases with increasing positive character of the aryl radicals. Tetraanisylhydrazine (m.p. 90.5°) dissolves in benzene even at ordinary temperatures with a light green colour, which is due to partial decomposition of the compound into dianisylamino radicals. On heating, the solution becomes a deep green, but lightens again on cooling.

The greatest tendency to dissociate, of all the tetraarylhydrazines investigated, was shown by tetra-[*p*-dimethylamino]-tetraphenylhydrazine, which was dissociated to the extent of 10% in benzene solution, and 21% in nitrobenzene solution, to bi-[dimethylamino]-diphenylamino:



The solutions are yellow.

Radicals with divalent nitrogen atoms have also been prepared from triarylhydrazines. If the hydrazine derivative I, obtained from diphenylhydrazine and trinitrochlorobenzene, is oxidized, blue-black crystals of compound II are formed (St. Goldschmidt):



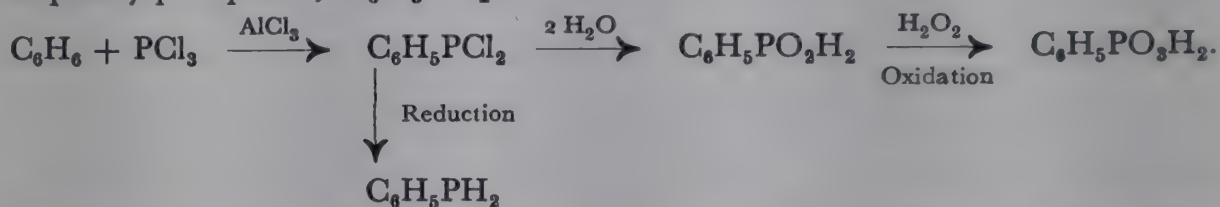
The latter is very stable, and dissolves with a permanganate-red colour. It can be reduced again to the original product and readily combines with triphenylmethyl, nitric oxide, bromine, etc.

CHAPTER 35. AROMATIC PHOSPHORUS, ARSENIC, AND ANTIMONY COMPOUNDS

Similar phosphorus, arsenic, and antimony compounds are found in the aromatic series to those in the aliphatic series. The methods by which they are obtained are, however, in part different, and particularly the aromatic arsenic compounds far exceed their aliphatic analogues in practical importance.

Phosphorus derivatives

Whilst aromatic arsonic acids (see below) and stibonic acids (see p. 503) are readily obtainable from diazonium salts, it has not yet been possible to replace the diazo-group by the phosphonic acid radical. However, benzene may be phosphorylated by an older method due to Michaelis, in which a mixture of the hydrocarbon and phosphorus trichloride is passed through a red-hot tube, or the two components are heated with anhydrous aluminium chloride. The product of the reaction is phenylphosphine dichloride, $\text{C}_6\text{H}_5\text{PCl}_2$. By the action of water it is hydrolysed to phenylphosphinic acid, $\text{C}_6\text{H}_5\text{PO}_2\text{H}_2$, which, on oxidation gives phenylphosphonic acid, $\text{C}_6\text{H}_5\text{PO}_3\text{H}_2$. On reduction phenylphosphine dichloride gives phenylphosphine, $\text{C}_6\text{H}_5\text{PH}_2$:



PHENYLPHOSPHINE, $\text{C}_6\text{H}_5\text{PH}_2$, has a composition analogous to that of aniline, but is completely different in its properties, in particular, being much less stable. It is a repulsive-smelling liquid, which is extremely readily oxidized. If it is mixed with an equivalent quantity of phenylphosphine dichloride, hydrogen chloride is eliminated and *phosphobenzene* formed:



The latter is a yellow amorphous powder, melting at 149° . In chemical structure and colour it corresponds to azobenzene; its chromophoric group is $-\text{P} = \text{P}-$.

Aromatic phosphorus compounds have some practical importance. Under the name tonophosphan, the sodium salt of *p*-dimethylamino-phenylphosphinic acid is used as a stimulant for metabolism (Benda).

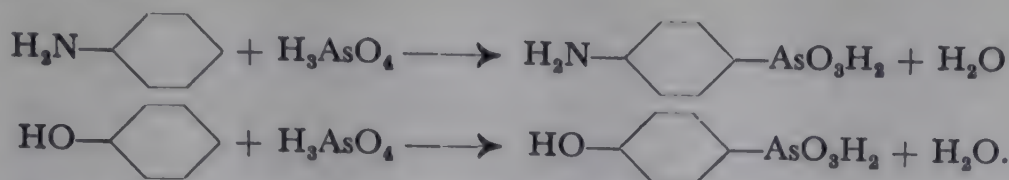
Arsenic compounds

There are several ways of synthesizing aromatic arsenic compounds. The method due to Michaelis, which depends on the reaction between diphenylmercury, and analogous mercury compounds, with arsenic trichloride, is now hardly ever used. It gives phenylarsine dichloride and its homologues:



The fusion of aromatic amines and phenols with arsenic acid is an important

method. From aniline, *p*-aminophenylarsonic acid is obtained, and from phenol, *p*-hydroxyphenylarsonic acid:



The process is analogous to the sulphonation of aromatic amines. In both cases unstable intermediate compounds are probably formed, such as sulphamic acids, and "arsamic acids", which contain the acid radical linked to the amino-group.

p-Aminophenylarsonic acid was first prepared in this way by Béchamps (1863). Its constitution was, however, not discovered until much later (P. Ehrlich).

Another important synthesis of aromatic arsonic acids starts with the diazonium salts, the diazo-group being substituted by the arsonic acid radical by the action of arsenious acid and its alkali-metal salts (see also p. 477):



This reaction, discovered by Barth, is capable of general application and has served for the preparation of a large number of aromatic arsonic acids.

By controlled reduction (e.g. with sulphurous acid) they give *arylarsonic oxides*, $\text{Aryl}\cdot\text{AsO}$, and by more energetic reduction (e.g. sodium hydrosulphite, or hypophosphorous acid) *arseno-compounds*, $\text{Aryl}\cdot\text{As}=\text{As}\cdot\text{Aryl}$. Particularly energetic reduction, e.g. prolonged treatment with nascent hydrogen, produced by the action of a metal on an acid, leads to *arylarsines*, ArylAsH_2 . (Triarylarsines are obtainable from arylmagnesium salts and arsenic trichloride; $(\text{C}_6\text{H}_5)_3\text{As}$ melts at 57°).

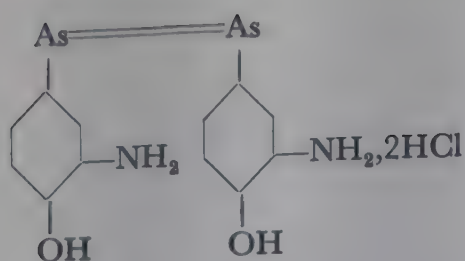
Various aromatic arsenic compounds have proved very effective for the treatment of infectious diseases,¹ particularly those produced by spirillæ and trypanosomes (P. Ehrlich). They therefore occupy a prominent place in medicine. According to P. Ehrlich those compounds with trivalent arsenic, especially certain arseno-compounds, are preferable to pentavalent arsenic compounds, since they combine greater effectiveness with relatively less injurious after-effects. There are, however, exceptions. It is possible that substances derived from pentavalent arsenic are only effective to the extent in which they are reduced to the trivalent stage in the body.

Of the large number of aromatic arsenic compounds known, the following are used in medicine: The sodium salt of *p*-aminophenylarsonic acid, *atoxyl*,



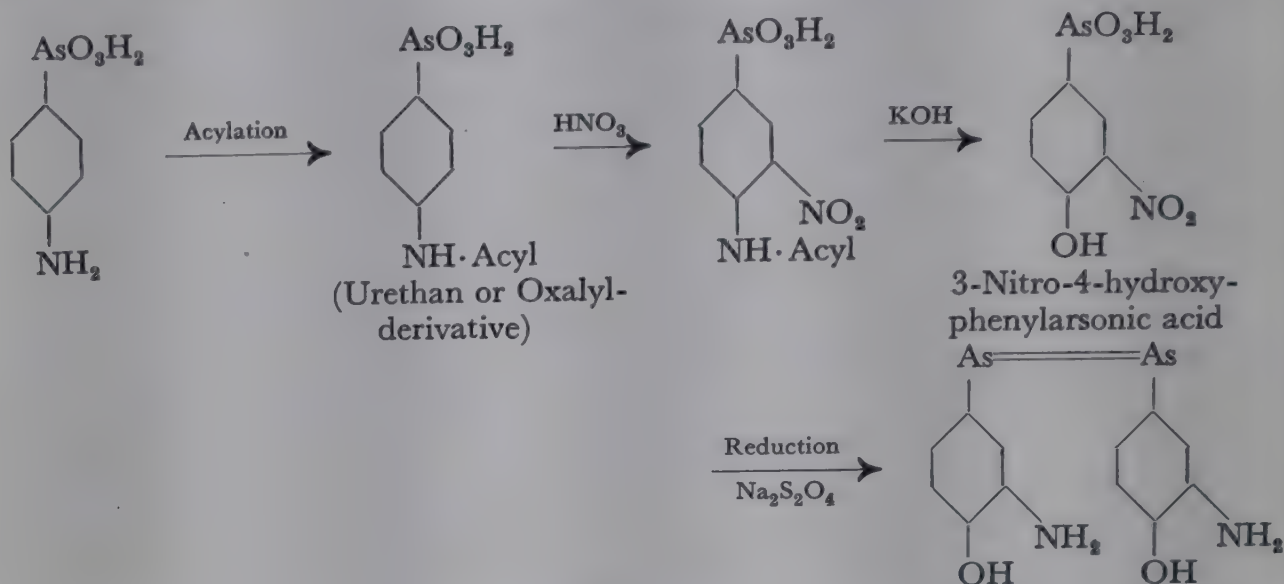
was used for the treatment of the tropical disease, sleeping sickness, being first employed for this purpose by Robert Koch. Owing to its toxic after-effects it is now little used. *Arsacetin*, acetylated *atoxyl*, $\text{CH}_3\text{CONH}-\text{C}_6\text{H}_4-\text{AsO}_3\text{HNa}$, acts in a similar way to *atoxyl*, but is somewhat less poisonous. *N*-phenylglycinamide-*p*-arsonic acid, *tryparsamide*, $\text{H}_2\text{N}\cdot\text{CO}\cdot\text{CH}_2\text{NH}-\text{C}_6\text{H}_4-\text{AsO}_3\text{H}_2$ (Jacobs and Heidelberger), is effective against sleeping sickness.

¹ VIKTOR FISCHL and HANS SCHLOSSBERGER, *Handbuch der Chemotherapie*. Teil I: Metallfreie organ. Verbindungen, Leipzig, (1932). Teil 2: Metallderivate. Leipzig, (1934).



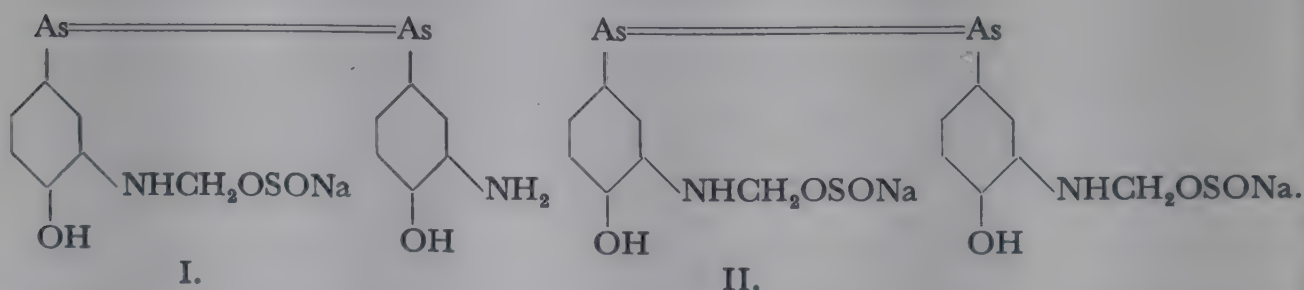
SALVARSAN, or ARSPHENAMINE, = 3:3'-diamino-4:4'-dihydroxyarsenobenzene hydrochloride. This most important arsenic preparation made by Ehrlich and Bertheim is widely used in the treatment of diseases due to spirochætes and trypanosomes, particularly syphilis. It is also effective against certain forms of malaria.

The synthesis of salvarsan starts from *p*-aminophenylarsonic acid, which is converted in a manner which will be readily followed from the scheme below into 3:3'-diamino-4:4'-dihydroxyarsenobenzene:



The salvarsan base is a light yellow amorphous substance, insoluble in water, but dissolving in hydrochloric acid or sodium hydroxide with salt formation. It is rather unstable, and is readily oxidized; it can therefore only be preserved in a vacuum or in an indifferent gas. It forms a characteristic, difficultly soluble sulphate.

NEOSALVARSAN is made from salvarsan and formaldehyde sulphonylate (q.v.). It is a mixture of substances of the formulæ I and II:



In contrast to the sodium salt of salvarsan, which, being a phenate, dissolves in water with an *alkaline* reaction, the solution of *neosalvarsan* is neutral.

Salvarsan combines with the salts of certain metals (silver, gold, copper) to form complex compounds, of which the silver compound has found practical use. Its spirillocidal effect appears to be even greater than that of salvarsan.

3-Acetylamino-4-hydroxyphenylarsonic acid has recently been used as a prophylactic and therapeutic agent against syphilis (stovarsol Fournau, spirocid).

Antimony compounds

The best way of obtaining aromatic *stibonic acids* is to make use of the reaction of diazonium compounds with salts of antimonous acid (see p. 477).

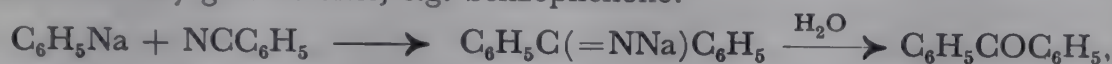


The stibonic acids give, on reduction, stibine oxides, aryl·SbO, and stibino-compounds, aryl·Sb=Sb·aryl. The latter are yellow-brown in colour, and are even more unstable than the arsenobenzene derivatives.

The activity of the aromatic antimony compounds is much less than that of the arsenic compounds, and they therefore find only occasional use in medicine, e.g. in cases of trypanosomiasis and (as the diethylamine salt of *p*-aminophenylstibonic acid = neostibosan) for kala-azar.

Aryl alkali-metal compounds

Aryl compounds of the alkali-metals are formed with unexpected readiness by the action of the alkali metals on chloro-substituted aromatic compounds in the presence of an indifferent organic solvent, at a temperature not higher than about 40°. The aryl alkali-metal compounds produced can be used for further reactions without isolating them, or they can be produced in the presence of suitable reagents which combine with them as they are formed. They react with carbon dioxide with formation of carboxylic acids; with benzonitrile they give ketones, e.g. benzophenone:



with sulphur dioxide they give sulphinic acids, and with acetic anhydride they form mixed aromatic-aliphatic ketones, etc. These compounds are therefore important starting substances for syntheses, resembling in this respect the alkylmagnesium salts.

Organic alkali-metal compounds of mixed aromatic-aliphatic hydrocarbons are also known. *Benzylsodium*, $\text{C}_6\text{H}_5\text{CH}_2\text{Na}$, and *triphenylmethylsodium*, $(\text{C}_6\text{H}_5)_3\text{CNa}$, are specially interesting on account of their red colour, and the fact that the sodium is linked ionically with the hydrocarbon radical.

Within recent times aromatic lithium compounds have been intensively investigated. H. Gilman succeeded in metalating numerous aromatic compounds with butyllithium, e.g. aryl ethers, primary, secondary, and tertiary aromatic amines etc. The entrance of Li into the aromatic nucleus mostly takes place in the *o*-position to the group containing the hetero-element:



Moreover, aryl bromides and iodides are often capable of exchanging their halogen atom for lithium (see p. 389). This also applies to iodo- and bromophenyl phenyl ether, *p*-bromoaniline, and similar substances, in which the halogen is replaced by lithium, by the action of butyllithium or phenyllithium.

Organic lithium compounds, when brought together with organic derivatives of other metals, very readily exchange organic groups with the latter. Equilibrium is established between the four possible organometallic compounds, e.g.



These reactions are reminiscent of the exchange of ions between electrolytes (Gilman).

By the action of phenyllithium on methyl benzyl ether and dibenzyl ether, respectively, phenylmethylcarbinol and phenylbenzylcarbinol are formed:



In these cases, therefore, an H-atom is set free in the benzyl ethers as a proton, whereupon the negatively charged ether radical rearranges to the alcoholate ion (G. Wittig).

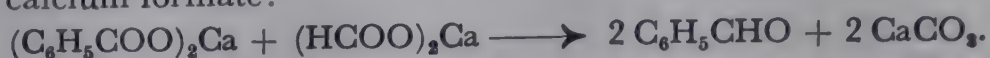
Section II

Compounds with di- and trivalent functions

CHAPTER 36. AROMATIC ALDEHYDES

Benzaldehyde, $\text{C}_6\text{H}_5\text{CHO}$, the simplest aromatic aldehyde is found in nature as the cyanogenetic glycoside *amygdalin*, which is contained in bitter almonds and the kernels of many fruits (apricots, peaches, etc.). Owing to hydrolysis it also occurs in these substances to a small extent in the free state. The smell of bitter almonds is due to it.

Benzaldehyde is formed similarly to the aliphatic aldehydes—by oxidation of benzyl alcohol, $\text{C}_6\text{H}_5\text{CH}_2\text{OH}$, and the distillation of a mixture of calcium benzoate and calcium formate:



Technically, however, it is usually prepared from toluene. This is oxidized with manganese dioxide and sulphuric acid in the presence of copper sulphate as catalyst. In this process the oxidation may easily be carried too far, with the production of benzoic acid. Chromyl chloride, CrO_2Cl_2 , however, will oxidize toluene essentially to the benzaldehyde stage.

Benzaldehyde is also obtained from benzal chloride, $\text{C}_6\text{H}_5\text{CHCl}_2$ (see p. 417), which is itself readily prepared by the chlorination of toluene. It is hydrolysed by milk of lime, lead oxide, or similar alkaline reagents.

Benzaldehyde is a colourless, oily liquid, which boils at 179° . Its characteristic smell of bitter almonds recalls that of nitrobenzene. Like the aliphatic aldehydes, benzaldehyde and its derivatives turn fuchsin-sulphurous acid red (for the mechanism of this reaction see p. 165), and reduce salts of the noble metals on warming. It gives a silver mirror with ammoniacal silver nitrate on boiling.

Atmospheric oxygen rapidly oxidizes ordinary, not perfectly pure benzaldehyde to benzoic acid. Closer study of this process by A. von Baeyer has not only elucidated the course of this particular reaction, but has, moreover, added much to our knowledge of self- or *autoxidation*. Benzaldehyde takes up primarily one molecule of oxygen forming unstable molecular oxides (or perbenzoic acid, $\text{C}_6\text{H}_5\text{CO}(\text{O}_2)\text{H}$?). Under ordinary conditions, however, these products rapidly break up again, giving oxygen in an active form, in addition to benzoic acid.

This active oxygen can now either convert further benzaldehyde molecules into benzoic acid, or, if other oxidizable substances are present, convert these into oxidation products. Thus, Baeyer observed that indigosulphonic acid, which is not affected by ordinary atmospheric oxygen, is oxidized in the presence of benzaldehyde. The aldehyde is thus acting here as an "activator", or "carrier" of oxygen.

Possibly the autoxidation of benzaldehyde is catalysed by heavy metals, and proceeds only when traces of heavy metals, especially iron, are present. Perfectly pure benzaldehyde does not show the phenomenon.

There are many analogies between the chemical properties of the aliphatic and aromatic aldehydes. Thus, benzaldehyde readily forms an oxime, $\text{C}_6\text{H}_5\text{CH}=\text{NOH}$ (benzaldoxime), a phenylhydrazone, $\text{C}_6\text{H}_5\text{CH}=\text{N}\cdot\text{NHC}_6\text{H}_5$, and a dif-

difficultly soluble, well-crystallized addition product, $\text{C}_6\text{H}_5\text{CH}(\text{OH})\cdot\text{SO}_3\text{Na}$, with sodium bisulphite.

On the other hand there are also certain differences between the aromatic aldehydes and their analogues of the aliphatic series. For example, when benzaldehyde and its derivatives are boiled with potassium cyanide solution, condensation occurs to α -hydroxyketones. From benzaldehyde itself, *benzoin* is formed:



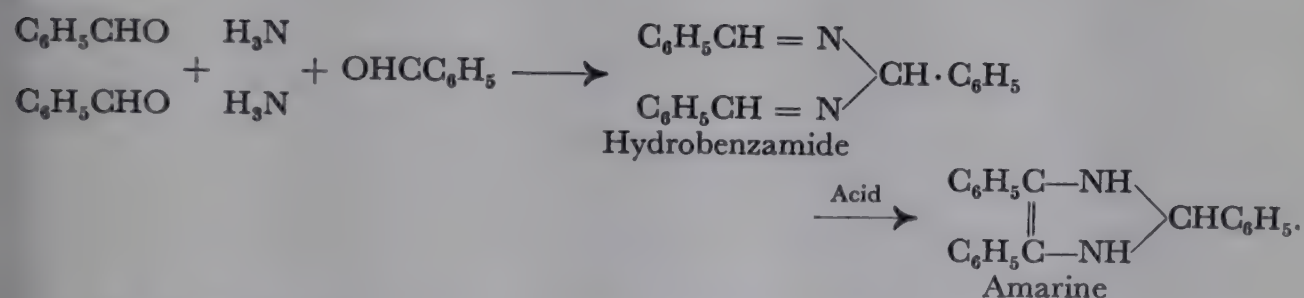
The active part of the potassium cyanide is the cyanide ion. In general, all the ionized salts of hydrocyanic acid may be used for such "benzoin condensations". However, the reaction can also be carried out in the absence of water, and in non-ionizing media. Under these conditions it has been possible to isolate an intermediate product in the form of an addition compound of benzaldehyde and sodium cyanide, $\text{C}_6\text{H}_5\text{CHO}\cdot\text{NaCN}$. The benzoin condensation is, however, limited to aromatic aldehydes, and is not given by those of the aliphatic series.

According to recent investigations by J. S. Buck and W. S. Ide, the benzoin condensation is a reversible reaction. The reconversion of benzoin into two molecules of benzaldehyde may be demonstrated if the compound is heated with another aldehyde and potassium cyanide in aqueous alcoholic solution. The following reaction takes place

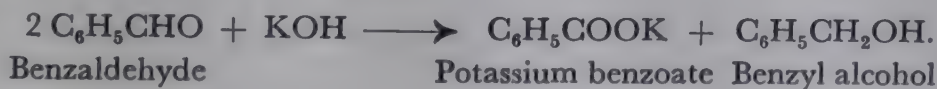


giving rise to a mixed benzoin.

Also, benzaldehyde reacts with ammonia in another way than do aliphatic aldehydes. Whilst the latter are converted into aldehydeammonias (p. 163), $\text{C}_n\text{H}_{2n+1}\text{CH}(\text{OH})\text{NH}_2$, and their decomposition products, three molecules of benzaldehyde combine with two molecules of ammonia to give *hydrobenzamide* (hydrobenzamide is converted on heating into the heterocyclic compound *amarine*):



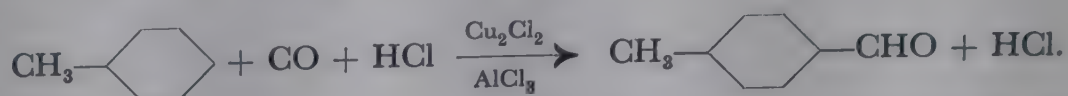
On boiling with alcoholic potash, benzaldehyde and its derivatives disproportionate into acid and alcohol:



These Cannizzaro reactions are also met with in connection with aldehydes of the aliphatic series, where they take place even in biological reactions. They usually occur, however, under other conditions (see p. 164).

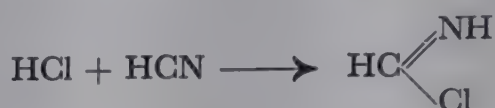
With phenols and tertiary aromatic amines (dimethylaniline) benzaldehyde readily condenses to give triphenylmethane derivatives. These reactions will be further considered in connection with the fuchsones (see p. 609) and Malachite green dyes (see p. 610). The manufacture of these dyes provides one of the principal uses of benzaldehyde. It is also used for the preparation of benzoic acid, and cinnamic acid, and in perfumery.

Other aromatic aldehydes. Gattermann has discovered a good method for the synthesis of homologues of benzaldehyde. It depends on the action of carbon monoxide and dry hydrogen chloride gas on aromatic hydrocarbons, in the presence of aluminium chloride and cuprous chloride. Carbon monoxide and hydrogen chloride react to give the (unknown) chloride of formic acid, HCOCl . The whole process is really a special case of the Friedel-Crafts synthesis of aromatic ketones (cf. p. 510). The aldehyde group usually takes up the *para*-position to the substituent present in the benzene nucleus:

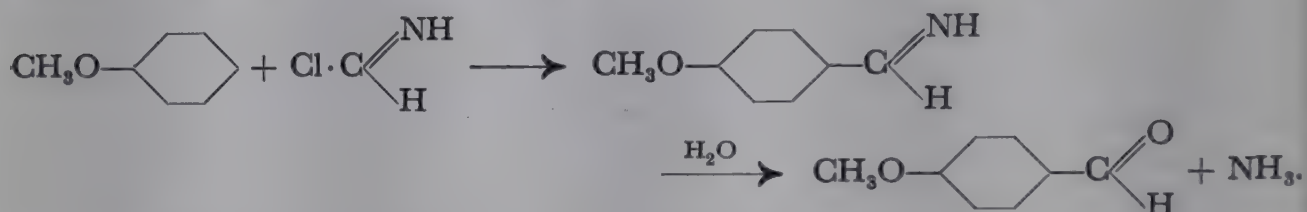


It was later discovered that benzene itself can react with carbon monoxide and hydrogen chloride in the presence of aluminium chloride to give benzaldehyde.

For the preparation of aldehydes of phenols and phenolic ethers the process is modified, a mixture of anhydrous hydrocyanic acid and hydrogen chloride being used in place of carbon monoxide and hydrogen chloride. The mixture reacts as the (unknown) imidochloride of formic acid:



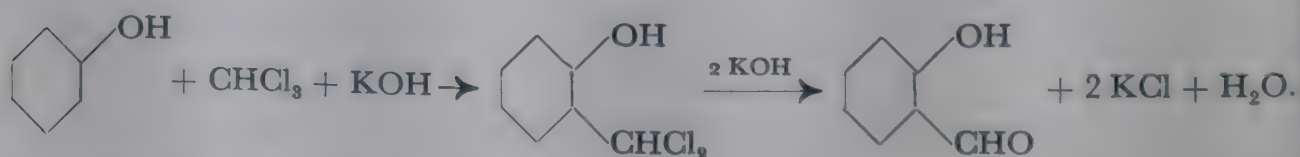
and forms an aldimine with the phenol or phenolic ether. These aldimines are usually hydrolysed to aldehydes and ammonia even by boiling water:



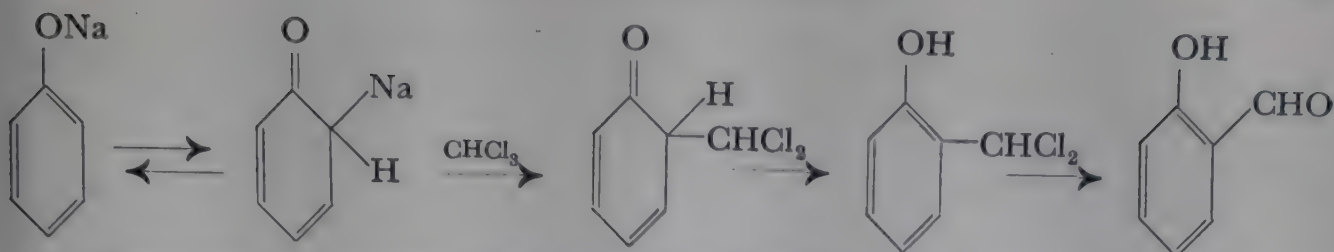
The smooth course of this reaction, and its extensive possibilities of application make it valuable as a preparative method. Polyhydric phenols with *meta*-hydroxyl groups (resorcinol, phloroglucinol, pyrogallol, etc.) react particularly readily with hydrocyanic acid and hydrogen chloride.

In the course of time various modifications of Gattermann's synthesis of phenolic aldehydes have been proposed. Thus the troublesome use of anhydrous hydrocyanic acid can be avoided by the use of dry cyanides, e.g. zinc cyanide, from which hydrocyanic acid is generated gradually during the reaction.

Another method of obtaining phenolic aldehydes, discovered by Reimer and extended by Tiemann, uses phenols, chloroform and alkali, and gives fairly good results:

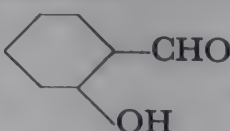


Usually *ortho*-hydroxy-aldehydes, together with smaller amounts of the *para*-isomers are obtained by this method. The reaction perhaps takes place in such a way, that sodium phenate reacts in the tautomeric form, *cyclohexadienone*-sodium, with chloroform (H. Gilman):

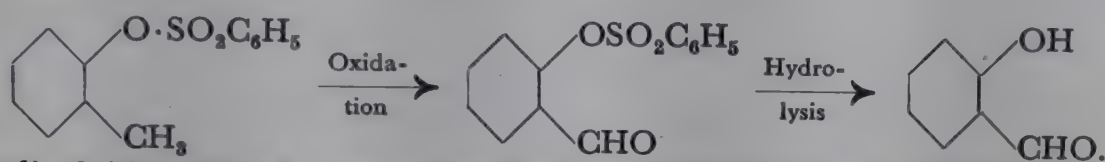


CINNAMIC ALDEHYDE, $\text{C}_6\text{H}_5\text{CH}=\text{CH}\cdot\text{CHO}$, is a constituent of many essential oils (oil of cinnamon, cassia oil, patchouli oil). It is a yellow liquid, b.p. 252° (with partial decomposition). Under 20 mm pressure it boils at 128° . Its strong smell of cinnamon makes it of use in perfumery. It is prepared artificially by condensation of benzaldehyde and acetaldehyde by means of alkali:



SALICYLALDEHYDE, , can be obtained by the Reimer-Tiemann

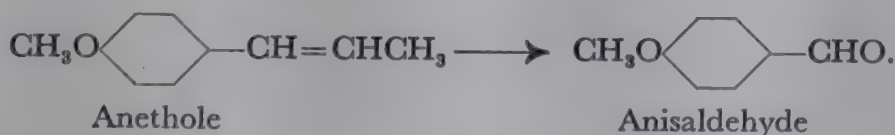
method from phenol, chloroform, and alkali. Technically it is prepared by the oxidation of arylsulphonic acid esters of *o*-cresol to the corresponding esters of salicylaldehyde. This is carried out in sulphuric acid solution by the action of manganese dioxide:



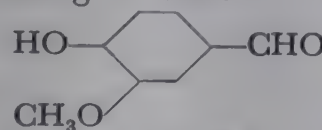
Salicylaldehyde is a pleasant smelling oil, boiling at 196° , and melting at 1.6° . It occurs naturally in certain species of *Spiræa*. It gives a violet coloration with ferric chloride. In industry, salicylaldehyde is used for the synthesis of coumarin and a few dyes.

The glucoside of salicylaldehyde has been obtained by the oxidation of salicin (see p. 451) with dilute nitric acid. It is called *helicin* and is of interest as an optically active aldehyde. For its use in the resolution of racemic amines into their optically active forms see p. 104.

ANISALDEHYDE, $\text{CH}_3\text{O}-\text{C}_6\text{H}_4-\text{CHO}$, an aldehyde frequently used in perfumery because of its aromatic smell, occurs in some essential oils (e.g. fennel oil), and can readily be prepared by the oxidation of anethole (see p. 434) with nitric acid, chromic acid, or ozone:



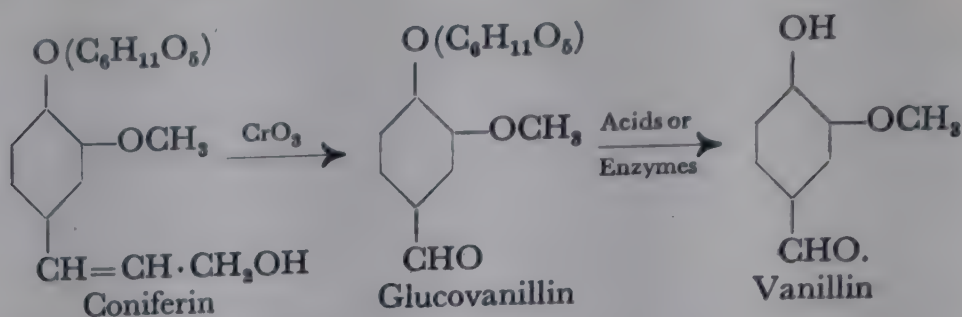
It is a liquid, boiling at 248° .

VANILLIN, . This aldehyde, of great importance as a

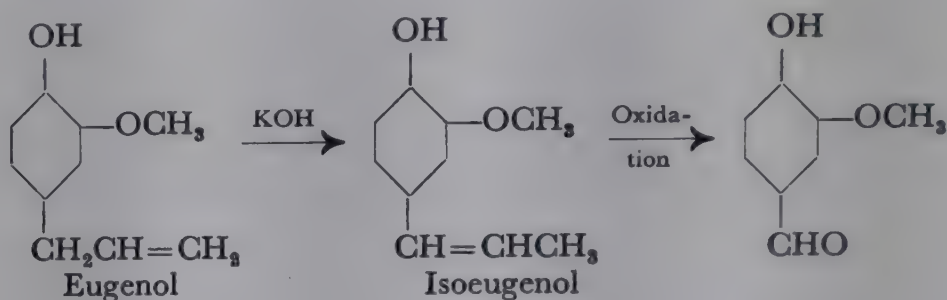
perfume, occurs widely spread in nature, but mostly, even in the vanilla pod, in small quantities. Probably it is contained in plants partly in the form of a glycoside.

Technically, vanillin is prepared either from natural products, chiefly eugenol, or synthetically from guaiacol.

Tiemann and Haarmann first obtained the compound from coniferin, a glucoside which is found in the sap of the cambium of conifers. On oxidation with chromic acid it gives glucovanillin, which is decomposed by acids or enzymes into vanillin and glucose:

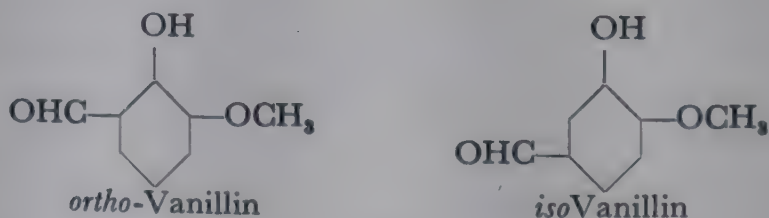


Although vanillin was made from coniferin in the 1870's this source is no longer of any importance for the technical production of vanillin. In its place the cheaper eugenol (see p. 435) is used. This may be directly oxidized to vanillin, but it is more convenient to convert the eugenol first into isoeugenol (q.v.) by means of alkali, and then to oxidize the latter:

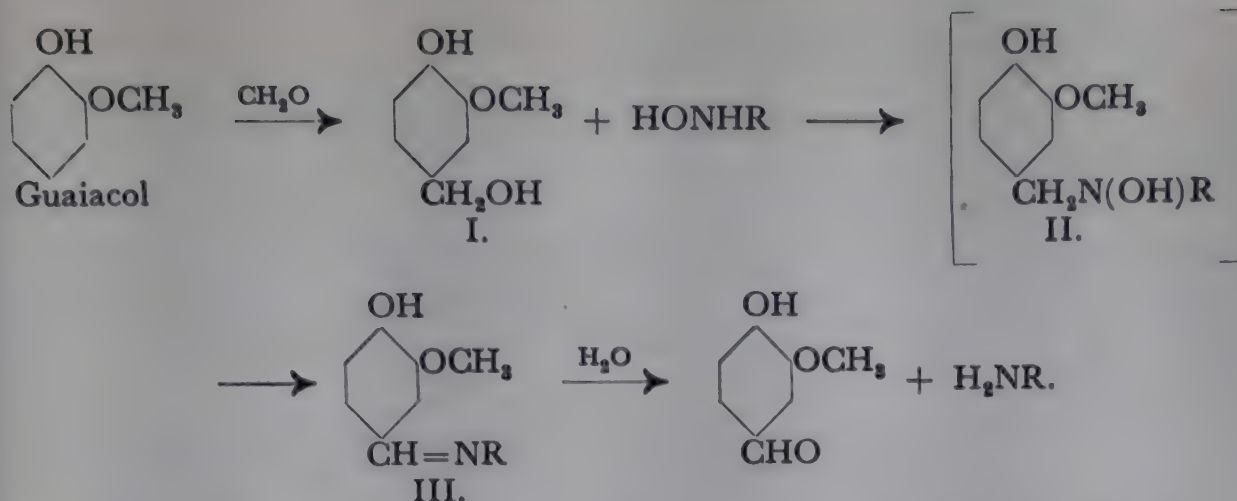


More recently a process has been worked out in which acetylisoeugenol, or even isoeugenol itself, suspended as a fine emulsion in water, is directly oxidized at low temperatures by ozone. The yield of vanillin is almost quantitative, and the product is very pure.

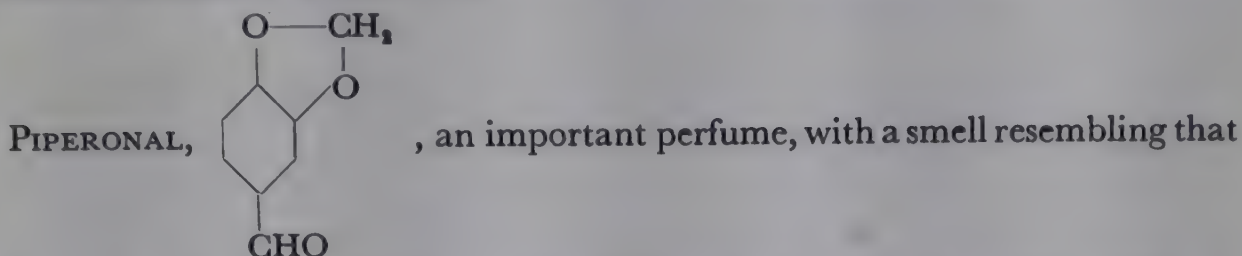
Syntheses of vanillin depending upon the introduction of the aldehyde group into the guaiacol molecule have received a large amount of attention as technical processes. A thorough treatment of them, however, is outside the scope of this book. It may be mentioned that vanillin, in addition to the so-called *ortho*-vanillin, and *isovanillin*:



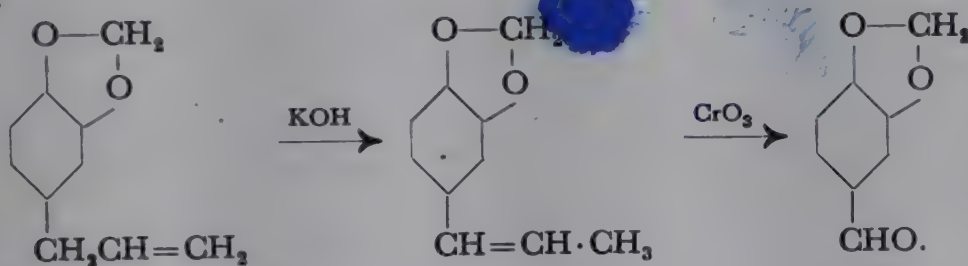
is formed by the Reimer-Tiemann reaction from guaiacol, chloroform, and alkali, and also by Gattermann's reaction from guaiacol, hydrocyanic acid, and hydrogen chloride. The method of Sandmeyer is of interest. Guaiacol is first made to react with formaldehyde, and the alcohol formed (I) is condensed with a hydroxylamine derivative through (II) to the benzylidene derivative (III), which is finally broken down by acids into vanillin and an amine:



Vanillin crystallizes in colourless needles, melting at $80-81^\circ$; b.p. 170° (15 mm). It colours ferric chloride solution blue.



of heliotrope, has been detected in small quantities in the oil of *Spiræa ulmaria*. It was formerly prepared technically by the oxidation of piperic acid (see p. 543). Piperonal is now always obtained from safrole (see p. 436). This is first isomerized by means of alkali to *isosafrole*, and the latter is oxidized by chromic acid to piperonal:



Piperonal melts at 36° , and boils at 263° .

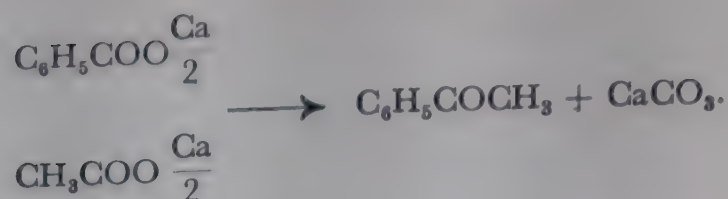
CHAPTER 37. AROMATIC KETONES

The aromatic ketones can be either purely aromatic, or mixed aliphatic-aromatic ketones. They can be prepared partly by methods similar to those used in the aliphatic series. The most important synthesis of aromatic ketones is, however, that of Friedel and Crafts (see below). Although an analogous process does exist for open-chain compounds (Hopff) it is usually not so straightforward, and has little importance as a method of preparation.

METHODS OF PREPARATION. 1. Ketones are formed, frequently in good yields, by the action of the chlorides of aromatic carboxylic acids on alkylzinc or alkyl-magnesium salts:

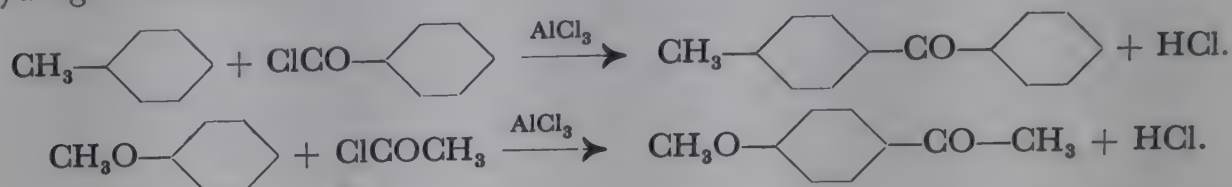


2. More important is the dry distillation of a mixture of the calcium salts of an aromatic acid and another carboxylic acid:

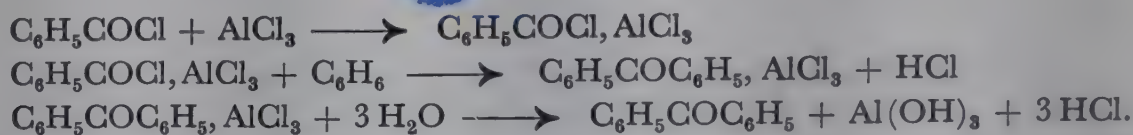


As a variation of this method, mixed aromatic-aliphatic ketones can be obtained by distilling a mixture of an aliphatic and an aromatic acid over heated thoria (about 450°). The thorium salts of the acids may be supposed to be intermediate products.

3. By the method of Friedel and Crafts, aromatic hydrocarbons or phenolic ethers (sometimes also those substituted by negative substituents, such as —NO₂, —COR, or —CN) react with acid chlorides in the presence of anhydrous aluminium chloride. Ketones are formed, usually very smoothly, with the elimination of hydrogen chloride¹:



This reaction may be carried out without a solvent, or with carbon disulphide, or some other indifferent liquid as solvent. The aluminium chloride takes part in the reaction. It forms a molecular compound with the acid chloride, which reacts with the hydrocarbon to give the ketone. The latter, however, remains at first combined with one molecule of aluminium chloride as an addition product, and is later decomposed by water (Perrier, Böeseken, Wieland):



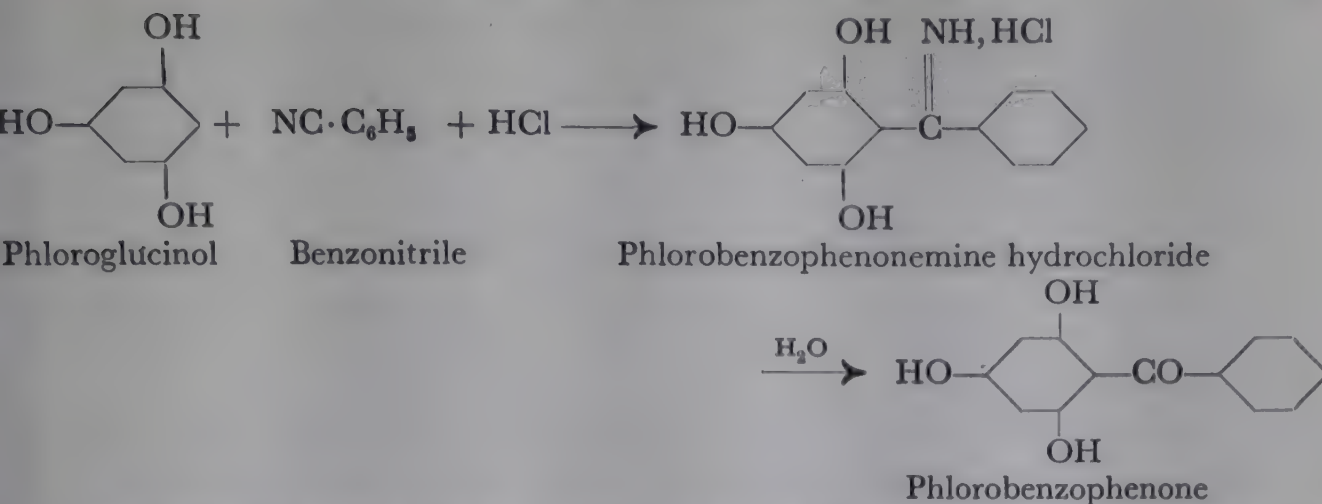
Hardly any limit can be imposed on the choice of the acid chloride used in this reaction. Aromatic and aliphatic acid halides of all kinds react readily. Carbonyl chloride, and the dichlorides of dicarboxylic acids, can react in a two-fold manner:



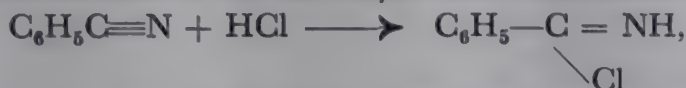
A synthesis of ketones analogous to the Friedel-Crafts reaction is the reaction between hydrocarbons or phenolic ethers, and acids, esters, or acid anhydrides and boron trifluoride. Thus, toluene, anisole, and phenol readily give the corresponding substituted acetophenones with acetic anhydride and boron trifluoride (H. Meerwein).

4. The process of J. Houben and K. Hoesch for the synthesis of aromatic hydroxy-ketones may be considered as an extension of Gattermann's synthesis of aldehydes (see p. 506). Polyhydric phenols, particularly those with hydroxyl groups in the *meta*-position, react with nitriles and dry hydrogen chloride gas with the formation of ketimines, which separate as crystalline hydrochlorides. On boiling with water they are hydrolysed to hydroxy-ketones. The condensation is usually carried out in ethereal solution:

¹ On the part played by aluminium chloride as a catalyst in organic chemistry, see GEORG KRÄNZLEIN, *Aluminiumchlorid in der organischen Chemie*, 3rd ed., Berlin, (1939). — C. A. THOMAS, *Anhydrous Aluminium Chloride in Organic Chemistry*, New York, (1945).



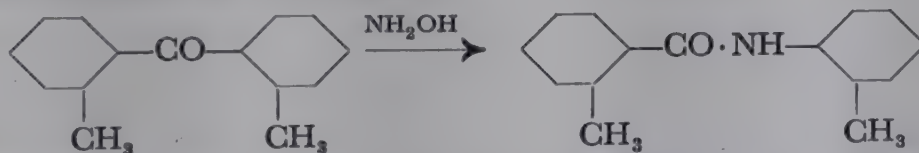
(The reaction takes place as follows: the nitrile and hydrogen chloride first combine to give the imido-chloride of the carboxylic acid concerned:



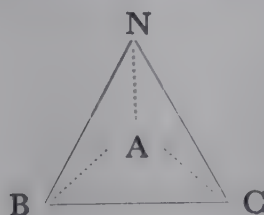
and the latter then condenses with the phenol with elimination of hydrogen chloride).

5. Aromatic hydroxy-ketones are also produced if the mono- or diesters of polyhydric phenols, e.g. resorcinol or hydroquinone, are heated with aluminium chloride, zinc chloride, magnesium chloride, and similar substances, sometimes in a solvent, such as nitrobenzene. An acyl radical migrates into the nucleus, and a second, if present, is eliminated.

PROPERTIES OF AROMATIC KETONES. The reagents for the carbonyl group met with in the aliphatic series, such as phenylhydrazine, semicarbazide, hydroxylamine, and the like, also react with very many aromatic ketones. In this way phenylhydrazones, semicarbazones, oximes, etc., are normally produced. It should, however, be noted that the CO-group enclosed between two aromatic radicals, shows a certain inertia to reaction. Thus, benzophenone, $\text{C}_6\text{H}_5\text{COC}_6\text{H}_5$, though it gives an oxime and a hydrazone, it does not give a bisulphite-addition compound, in contrast to aliphatic ketones. If there are two substituents in the *ortho*-positions with respect to the carbonyl group, as in *o,o'*-dimethylbenzophenone, the steric hindrance is so great that oxime-formation is also prevented, and if any reaction can be made to take place between the ketone and hydroxylamine, rearrangement occurs to an acid amide:



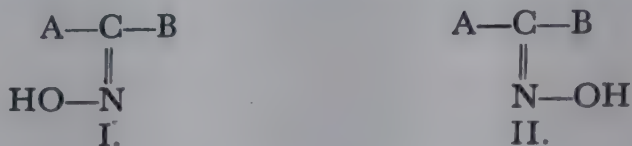
The oximes of unsymmetrical aromatic ketones exist in two stereoisomeric forms, which are known as *syn*- and *anti*-forms. To explain their existence, Hantzsch and Werner put forward the following theory in 1891. It is still regarded as correct. The nitrogen atom can, under certain circumstances, leave the plane in which its three valencies lie. It takes up its position at the apex of a tetrahedron, at the other three apices of which lie the atoms linked to the nitrogen:



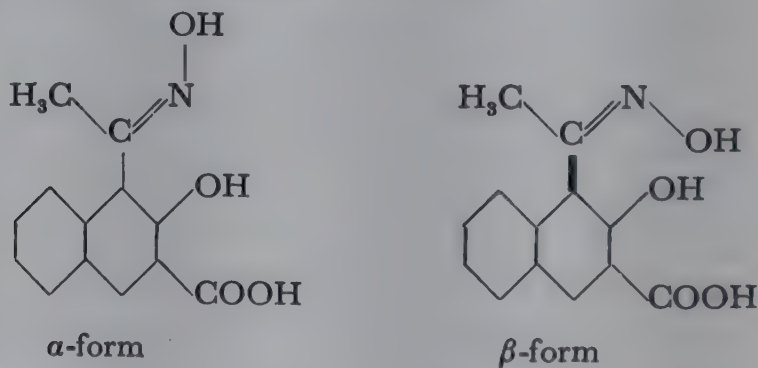
If a nitrogen atom is linked by *two* of its valencies to a carbon atom carrying two different substituents, there are two possible orientations for the nitrogen tetrahedron:



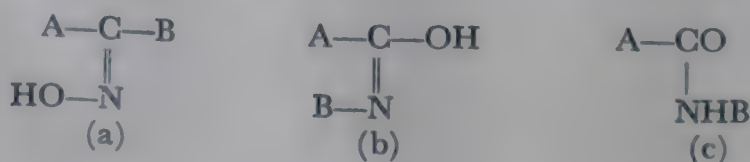
Thus, the hydroxyl group attached to the third nitrogen valency can lie in the neighbourhood of either A or B. This type of isomerism is found in the oximes of unsymmetrical aromatic ketones, which possess the following projection formulæ:



A proof of the correctness of the Hantzsch-Werner theory is provided by the observation of Meisenheimer that the oxime of 1-aceto-2-hydroxy-3-carboxynaphthalene exists in two forms (α and β), of which the β -isomeride gives optically active alkaloid salts; the latter, however, racemize rapidly. The asymmetric structure of the β -form (as in the case of the optically active biphenyl derivatives, p. 396) is due to restricted rotation of the naphthalene nucleus about the axis printed below in heavy type, this, in turn, as a result of the nearness of the two OH-groups in the β -form.



The ketoximes undergo a peculiar rearrangement into acid amides, when treated with concentrated sulphuric acid, phosphorus pentachloride in ether, or benzenesulphonyl chloride in pyridine. This was discovered by Beckmann and is known as the "Beckmann rearrangement". In the first phase of the reaction, the hydroxyl group of the oxime changes places with one of the organic radicals A or B. Whilst the view has been held until recently that this change of places occurred between the hydroxyl group and the *neighbouring* radical (in formula I above, between OH and A, and in II, between OH and B), more recent investigations by Meisenheimer have shown that as a rule it is just the reverse. The compound (b) formed by rearrangement of the oxime (a) is none other than the enol form of an acid amide. The product of the rearrangement may therefore also be written as (c):



It appears that the reagents added to bring about the rearrangement first esterify the hydroxyl group of the oxime, the transformation taking place with the oxime ester $ABC = NO \cdot X$.

An example of stereoisomeric ketoximes is furnished by the two *monoximes of benzil*, $C_6H_5CO \cdot COC_6H_5$:

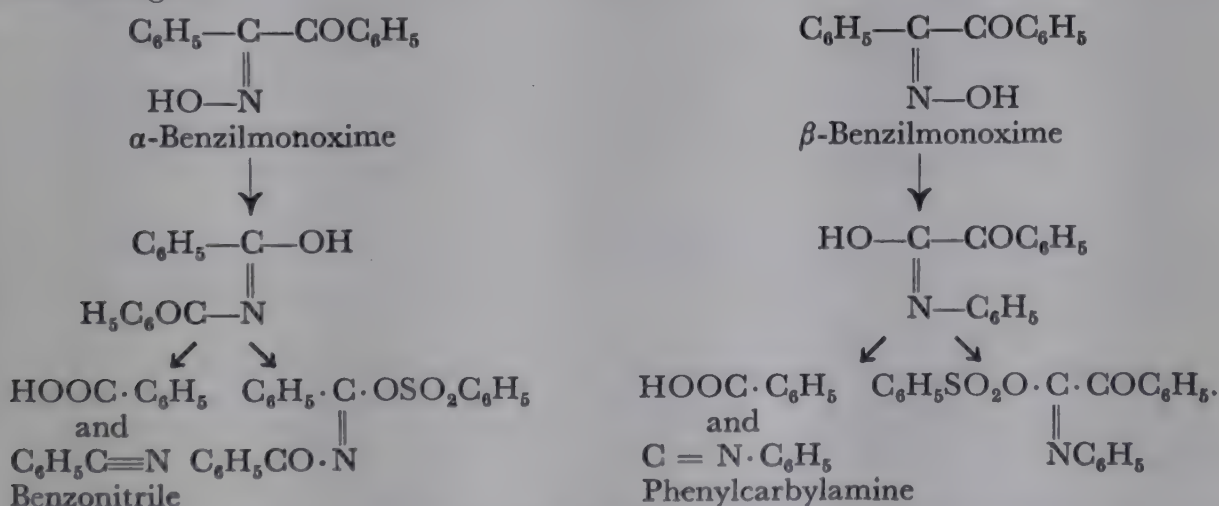


They are distinguished as the α -form (m.p. 138°), and the β -form (m.p. 113°). The configuration of the β -isomeride is established by the fact that its benzoyl derivative is obtained by the oxidation of triphenylisoxazole with ozone (Meisenheimer):



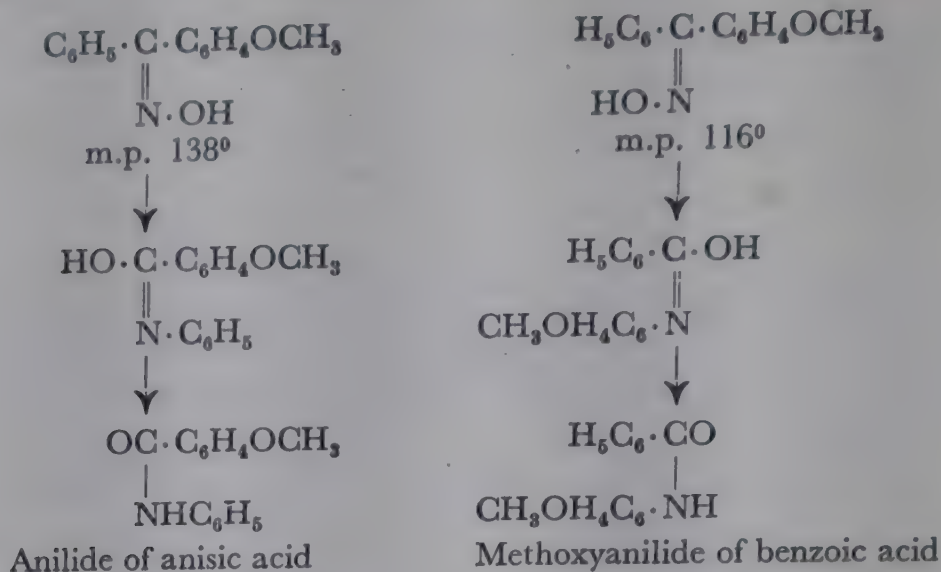
Since the group attached to the nitrogen in the original substance (triphenylisoxazole) is in the *cis*-position to $-C \cdot C_6H_5$, and in the *trans*-position to the phenyl radical, this must also be the case for the degradation product, benzoyl- β -benzilmonoxime. It also follows that of the two formulæ of the isomeric benzilmonoximes given above, 1 represents the configuration of the α -compound, and 2 that of the β -compound.

In the Beckmann rearrangement (carried out with benzenesulphonyl chloride in pyridine) part of the α -benzilmonoxime is broken down to benzonitrile, whilst the β -isomeride, under the same conditions, gives phenylcarbylamine. The reactions leading to these degradation products are shown in the following scheme. The conversion of the α -oxime into benzonitrile shows that the Beckmann rearrangement of this compound is bound up with the migration of the benzoyl radical C_6H_5CO to the nitrogen, whilst the formation of phenylcarbylamine from β -benzilmonoxime can only be due to the migration of the phenyl group, C_6H_5 , to the nitrogen:



As a further example of stereoisomeric ketoximes the two *p*-methoxybenzophenone oximes may be mentioned, one of which melts at 138° and the other at 116° . The Beckmann rearrangement of the first gives rise to the anilide of anisic

acid, whilst that of the isomeride melting at 116° gives the methoxyanilide of benzoic acid:



It is clear that the Beckmann rearrangement of stereoisomeric ketoximes enables their configurations to be arrived at. This supposes, however, that the change of places of the hydroxyl group with the organic radical *always* takes place in the same way. As mentioned above, in most cases it appears that the organic group not neighbouring the hydroxyl migrates and attaches itself to the nitrogen atom. However, it has not been possible in all cases to carry out control experiments. It is also believed that the Beckmann rearrangement proceeds sometimes according to the older view, i.e. that there is a change of place of neighbouring groups, and that according to the nature of the compound the one or other possibility actually occurs.

Also with *aldoximes* — especially those of the aromatic series — both of the possible forms, the *syn*- and the *anti*-isomers, are frequently met with:

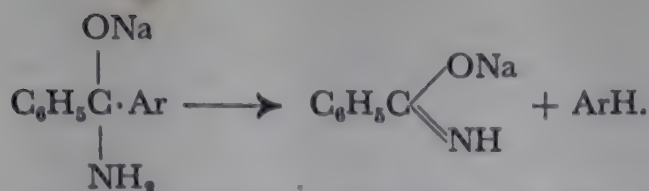


For example, the two forms of benzaldoxime melt at 81° and 49° respectively. The configuration of the two isomers cannot always be established with ease or with certainty. The general opinion used to be that the isomer which readily splits off water and thereby changes into a nitrile, represented the *syn*-form. According to investigations by Taylor, R. Hauser, and others, however, the contrary usually appears to be the case, namely, that it is generally the *anti*-form which loses water by the action of alkalis, thus producing a nitrile.

Individual ketones. ACETOPHENONE, $\text{C}_6\text{H}_5\text{COCH}_3$. This substance is a constituent of coal-tar. It melts at 19.6° . It is a hypnotic, and was formerly used as such under the name hypnone.

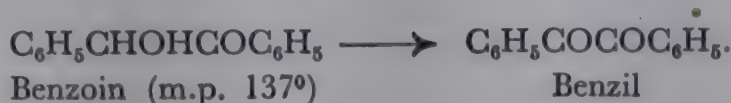
BENZOPHENONE, $\text{C}_6\text{H}_5\text{COC}_6\text{H}_5$, exists in two modifications, of which one is very unstable, forms monoclinic crystals, and melts at 27° , whilst the other is completely stable, and forms rhombic crystals melting at 49° .

As Haller has shown, ketones of the type $\text{C}_6\text{H}_5\text{COAryl}$ will add one molecule of sodamide, and the addition product decomposes at the temperature of boiling benzene or toluene, in which the reaction is carried out, into an acid amide (or its sodium salt) and a hydrocarbon (Schönberg):



This reaction provides in some cases a very suitable method of degradation for such ketones.

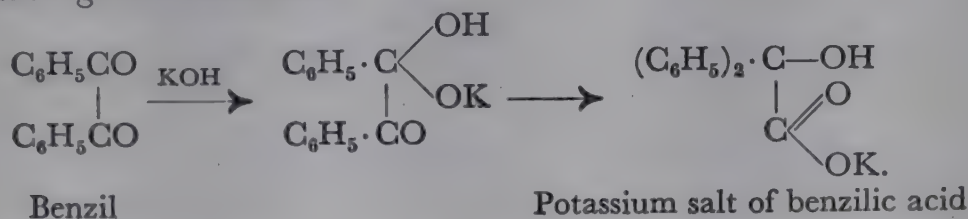
BENZIL, $\text{C}_6\text{H}_5\text{COCOC}_6\text{H}_5$. This is the simplest purely aromatic diketone. It is yellow in colour, and melts at 95° . It is readily obtained by oxidation of benzoin, which itself is prepared from benzaldehyde by the benzoin condensation (see p. 505):



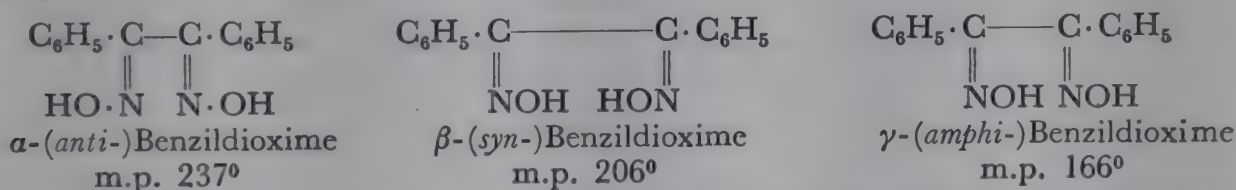
Reducing agents convert benzil and benzoin into desoxybenzoin, $\text{C}_6\text{H}_5\text{CH}_2\text{COC}_6\text{H}_5$ (m.p. 60°). This compound contains a reactive methylene group (standing between carbonyl and phenyl!), which can be alkylated by the action of an alkyl iodide and alkali:



Benzil undergoes an important change when fused with alkalis. It is converted, apparently after first adding on a molecule of alkali, into a hydroxy-acid, benzilic acid. The process is known as the "*benzilic acid rearrangement*", and has been observed with many analogous substances:

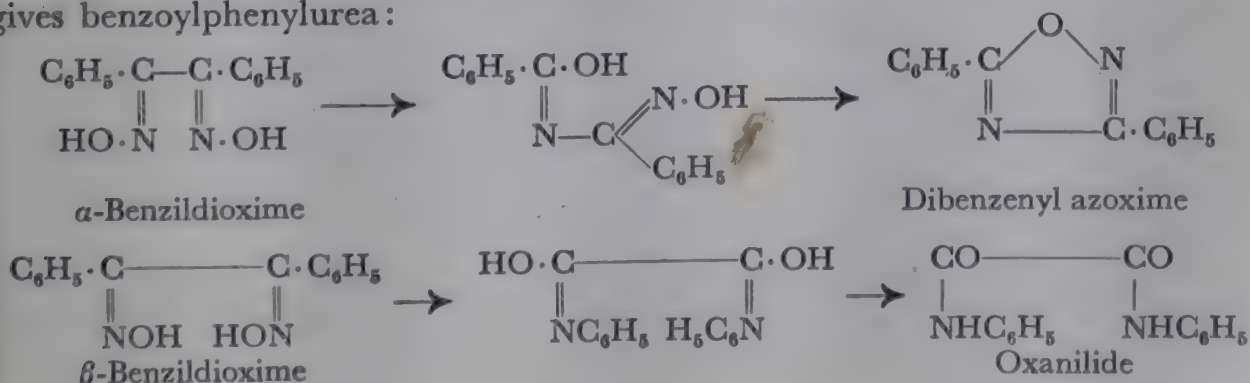


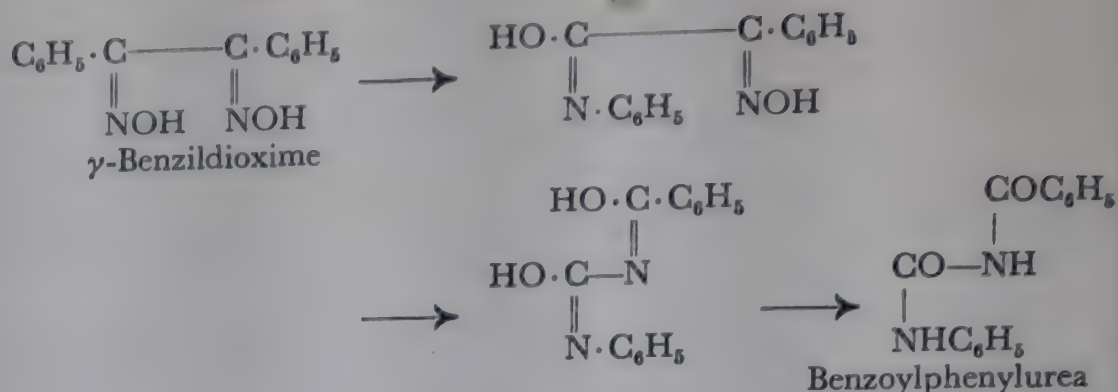
The dioxime of benzil occurs in three stereoisomeric forms, as required by theory. Their formulæ are:



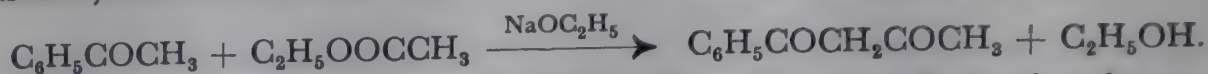
The *syn*-compound readily forms an anhydride, a fact which is connected with the proximity of the two hydroxyl groups.

The three benzildioximes give different reaction products when submitted to the Beckmann rearrangement. The α -form gives a heterocyclic compound, dibenzenyl azoxime; the β -form gives the anilide of oxalic acid; γ -benzildioxime gives benzoylphenylurea:

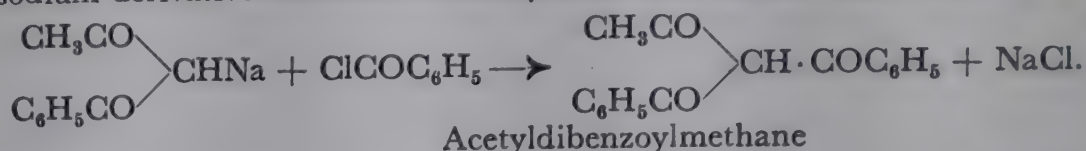




BENZOYLACETYL METHANE, $\text{C}_6\text{H}_5\text{COCH}_2\text{COCH}_3$ (benzoylacetone), m.p. 61° , is obtained by condensation of acetophenone with acetic ester by means of sodium alcoholate:



It contains a reactive methylene group (standing between two carbonyl groups!) When its sodium derivative reacts with benzoyl chloride, *acetyldibenzoylmethane* is formed:



Acetyldibenzoylmethane exists in an enol and a keto form, both of which have been isolated in the pure state. The enol form melting at $101\text{--}102^\circ$ is acid, and soluble in alkalis. It gives a red coloration with ferric chloride. The keto form has a melting point of $107\text{--}110^\circ$, and only dissolves in alkalis on long shaking (during which it is converted into the enol form). It does not give a coloration with ferric chloride. The enol form is unstable, and isomerizes to the keto-compound, particularly on warming.

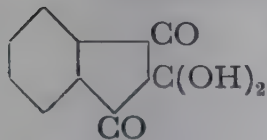
Other triacetylmethanes are known either only as the keto or only as the enol form (Claisen).

The following aromatic poly-ketones have more than two adjacent carbonyl groups:

DIPHENYLTRIKETONE, $\text{C}_6\text{H}_5\text{CO} \cdot \text{CO} \cdot \text{COC}_6\text{H}_5$, golden-yellow crystals, m.p. 70° . Forms a colourless hydrate (m.p. 90°).

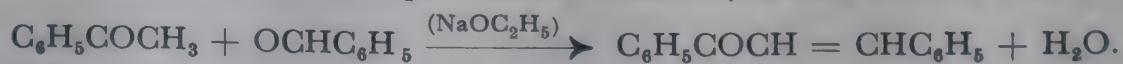
DIPHENYLTETRAKETONE, $\text{C}_6\text{H}_5\text{CO} \cdot \text{CO} \cdot \text{CO} \cdot \text{COC}_6\text{H}_5$, a red compound, which combines with water to give a yellow hydrate, m.p. 87° .

TRIKETOHYDRINDENE HYDRATE, or "NINHYDRIN", has some importance as a reagent for amino-acids, with which it gives an intense blue colour on boiling in aqueous solution. The reaction is very sensitive. It will detect glycine, for example, at a dilution of 1 : 5,000.



Unsaturated ketones. Unsaturated aromatic ketones are usually prepared by the condensation of aromatic aldehydes with acetophenone, acetone, and similar compounds. Alkalis or hydrogen chloride may be used as condensing agents.

Thus, BENZALACETOPHENONE, $\text{C}_6\text{H}_5\text{COCH} = \text{CHC}_6\text{H}_5$, also known as *chalkone*, is obtained from acetophenone, benzaldehyde and sodium ethylate:

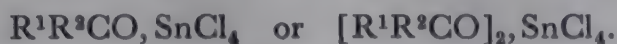


It is a yellow solid melting at 58° , and boiling at $345\text{--}348^\circ$.

In a similar way DIBENZALACETONE, $\text{C}_6\text{H}_5\text{CH} = \text{CH} \cdot \text{CO} \cdot \text{CH} = \text{CHC}_6\text{H}_5$, is obtained from two molecules of benzaldehyde and one molecule of acetone. It forms light yellow tablets, m.p. 112° .

DICINNAMYLIDENEACETONE, $\text{C}_6\text{H}_5\text{CH} = \text{CH} \cdot \text{CH} = \text{CH} \cdot \text{CO} \cdot \text{CH} = \text{CH} \cdot \text{CH} = \text{CHC}_6\text{H}_5$, obtained from cinnamic aldehyde and acetone, is golden yellow, and melts at 142° .

These unsaturated ketones show beautiful "*halochromic*" effects. By this is meant colour reactions produced by the action of acids or certain metallic salts on the compounds. The cause of these effects is the formation of molecular compounds. Those compounds of unsaturated ketones with stannic chloride have been particularly investigated (P. Pfeiffer). They have the formulæ:



Amongst the addition products of ketones and acids, the perchlorates, $R^1R^2CO, HClO_4$, stand out for their relative stability and ease of crystallization.

The unsaturated ketones always dissolve in concentrated sulphuric acid forming solutions of a deeper colour than that of the ketones themselves. The reason for this halochromism is again the formation of addition products of the ketone and sulphuric acid. The colour of a solution of dibenzalacetone in concentrated sulphuric acid is orange, and of dicinnamylideneacetone in the same acid, violet.

The observation made by Tschelinzeff, that unsaturated ketones of the chalcone type can react with aldehydes in the presence of 60 per cent sulphuric acid, exchange of aldehyde radicals taking place, is noteworthy:



It is possible that ketones of the type $H_3C \cdot CO \cdot CR_3$, are formed as intermediate products in the reaction.

Hydroxy-ketones. Many of the aromatic hydroxy-ketones are naturally-occurring substances. They are wide-spread in the vegetable kingdom, either free, or as glycosides. Several of them have dyeing properties, and form the colouring matters of flowers and dye-woods.

p-HYDROXYACETOPHENONE, $HO-\text{C}_6\text{H}_4-\text{COCH}_3$, melts at 107° , and is found in

the form of the glucoside picein, $(C_6H_{11}O_5)O-\text{C}_6\text{H}_4-\text{COCH}_3$, in the needles of the silver-fir and in willow-bark.

o-HYDROXYACETOPHENONE, $\text{C}_6\text{H}_4(\text{OH})-\text{COCH}_3$, occurs in the wood oil of *Chione glabra*. It boils at 213° .

RESACETOPHENONE, $HO-\text{C}_6\text{H}_3(\text{OH})-\text{COCH}_3$, made from resorcinol, glacial acetic

acid, and zinc chloride, melts at 142° ; its 3:5-dimethyl derivative, *clavatol*, is present in *Aspergillus clavatus*.

PÆONOL is the monomethyl ether of resacetophenone.

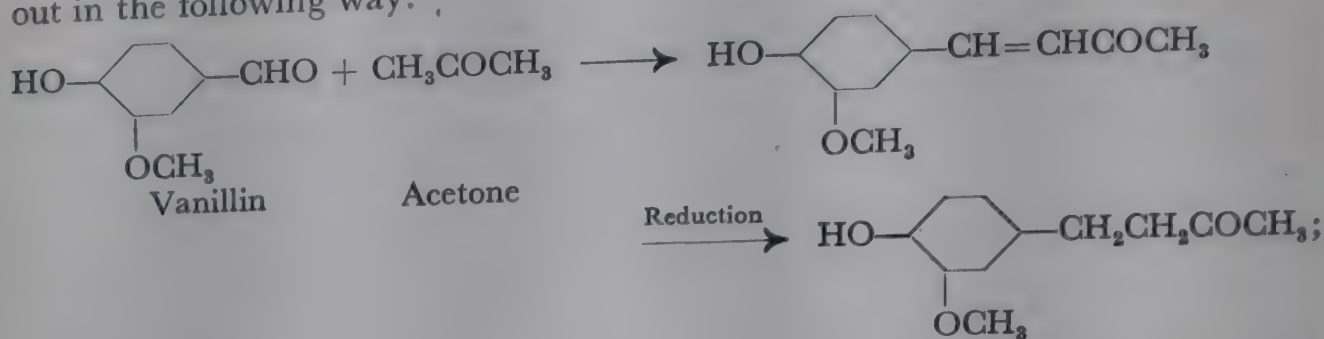


It is found as a glycoside in the root bark of various species of pæony.

APOCYNIN, $HO-\text{C}_6\text{H}_3(\text{OCH}_3)-\text{COCH}_3$ (from *Apocynum cannabinum*), is a heart stimulant and diuretic.

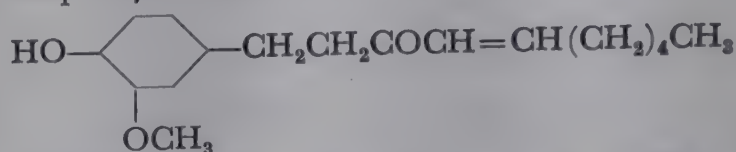
ZINGERONE, , is a sharp-tasting constituent of

ginger. Its constitution has been elucidated by Nomura, and the synthesis carried out in the following way:

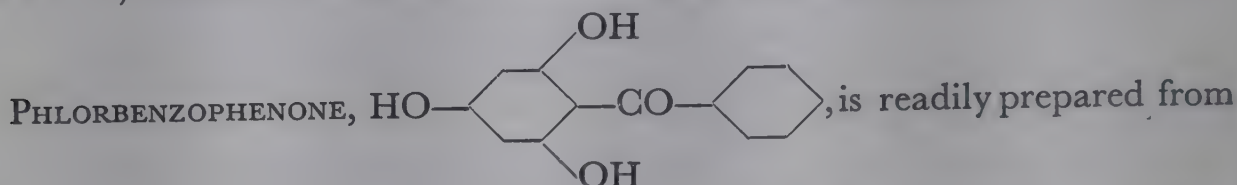


Zingerone melts at 41° .

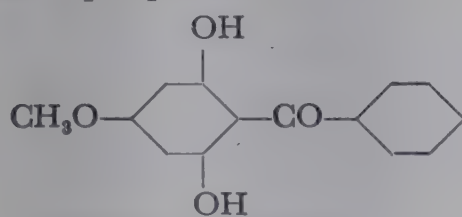
Another sharp-tasting principle of ginger is SHOGAOL, [4-hydroxy-3-methoxyphenyl]-ethyl $\Delta^{\alpha,\beta}$ -heptenyl ketone:



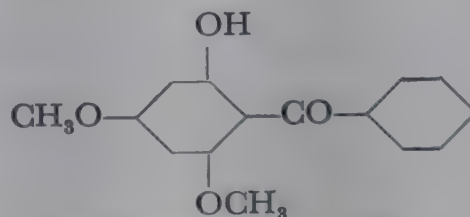
PHLORACETOPHENONE DIMETHYL ETHER, ($\text{OCH}_3 : \text{OCH}_3 : \text{OH} : \text{COCH}_3 = 1 : 3 : 5 : 4$) occurs in various essential oils (e.g. in that of *Blumea balsamifera*).



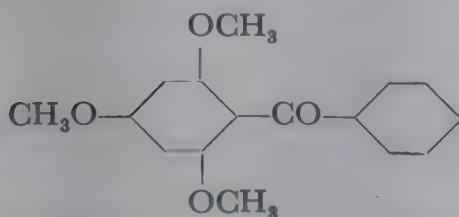
phloroglucinol, benzonitrile, and hydrogen chloride, by the method of K. Hoesch and Houben. It is the parent substance of the "cotoins". This is a group of closely related substances, comprising cotoin, hydrocotoin, methylhydrocotoin, protocotoin, and methyl-protocotoin, which are found in coto bark, the bark of a species of *Lauraceae*, and which are used medicinally in the treatment of diarrhoea and outbreaks of perspiration:



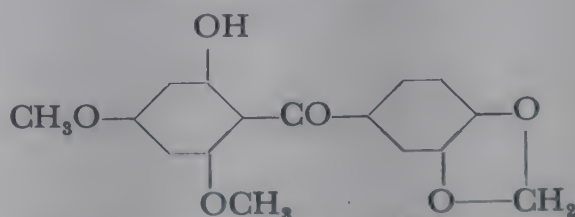
Cotoin, m.p. 131°



Hydrocotoin, m.p. 98°

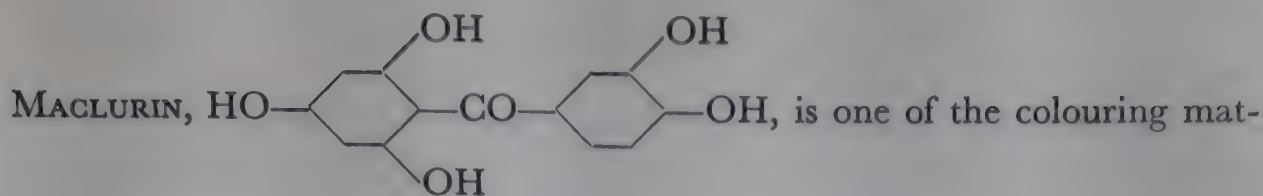


Methylhydrocotoin, m.p. 115°



Protocotoin, m.p. 141°

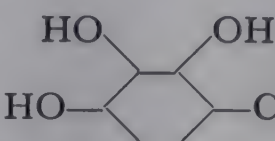
Cotoin has been synthesized by the partial methylation of phlorbenzophenone with diazomethane, and artificial methods for preparing hydrocotoin, methylhydrocotoin, and protocotoin are also known.

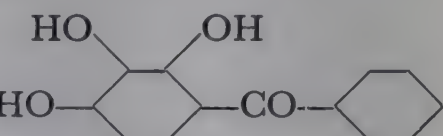


ters of yellow wood (fustic) (i.e. the stem wood of *Morus tinctoria*) where it occurs together with morin (see p. 558), another yellow-coloured substance. Maclurin crystallizes in yellow columns, and when anhydrous melts at 200°.

The compound can be prepared artificially by the condensation of phloroglucinol with protocatechuic nitrile and hydrogen chloride.

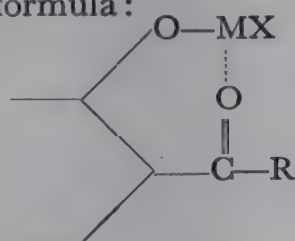
Extract of fustic is used for the dyeing of cotton which has been mordanted with alum, iron, or copper mordants. Chrome-mordanted wool is also dyed by it. The important dye-component of fustic is morin (see p. 558); maclurin, is not suitable for dyeing.

GALLACETOPHENONE, ALIZARIN YELLOW C, , is produced synthetically by heating a mixture of pyrogallol, glacial acetic acid, and zinc chloride. It is a pale yellow mordant dye. The aluminium lake is intensely yellow, and the chromed dye has an olive-green colour.

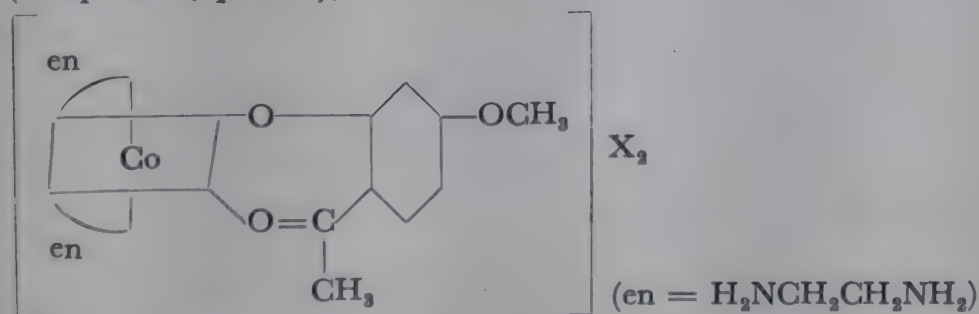
GALLOBENZOPHENONE, ALIZARIN YELLOW A,  This is prepared in a similar way to the above compound by heating pyrogallol, benzoic acid, and zinc chloride. The dye gives yellow shades, which are fast to light and washing, on calico with an aluminium mordant.

Liebermann and Kostanecki have shown that hydroxy-ketones which contain two hydroxyl groups adjacent to the CO group are usually good *mordant dyes* (see alizarin, p. 592), i.e. they form coloured metal lakes.

These metal lakes are, according to A. Werner internal complex salts, corresponding to the general formula:



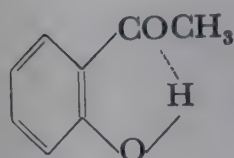
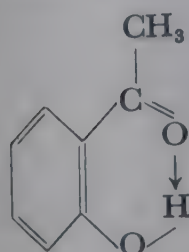
i.e. the metal is doubly linked to the organic component. The definite proof of this was supplied by P. Pfeiffer in the case of the cobalt salts of diethylenediamino-pæonol (see pæonol, p. 517),



which could be resolved into optically active forms. This appears only to be possi-

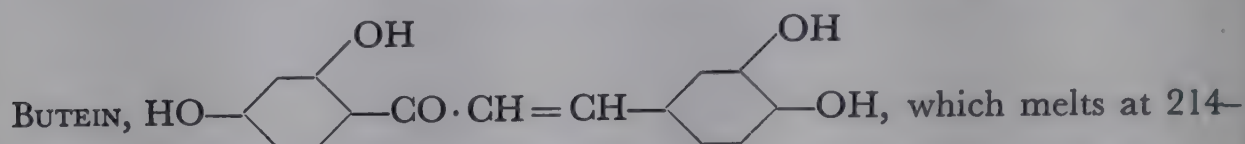
ble if the pæonol radical occupies two coordination positions, and if the compound has the spatial formula shown above.

An interaction between the H-atom of the hydroxyl-group and the carbonyl group also occurs in the free *o*-hydroxy-ketones and analogous compounds. The H-atom forms a hydrogen bridge between the oxygen of the hydroxyl group and that of the carbonyl group. This phenomenon is known as *chelation*. According

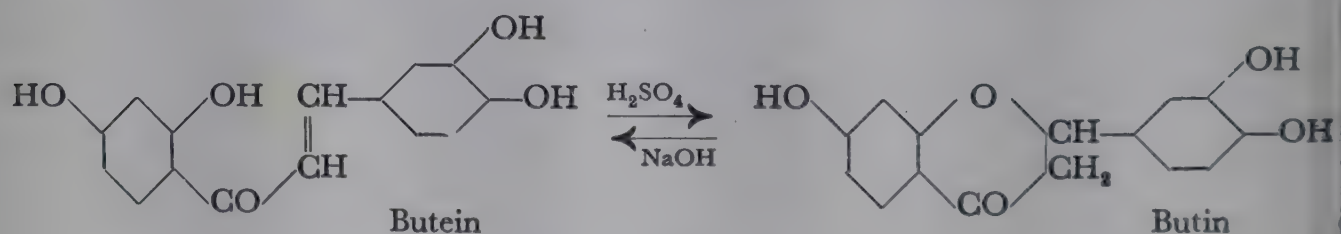


to the electronic theory, the hydrogen atom of the hydroxyl group also takes part in the electron system of the carbonyl oxygen atom, by adding to a lone electron pair (see p. 127). The extent of the formation of chelate structures depends on the constitution of the substance. It exerts a great influence, especially on the physical properties of the compounds (solubility, absorption spectrum, etc.), and can even affect their chemical behaviour (e.g. substitution processes).

The infra-red absorption spectra of compounds containing hydrogen bonds lack the band at 2.7μ which is characteristic of OH-groups, and in its place there is often a band at 3.3μ .

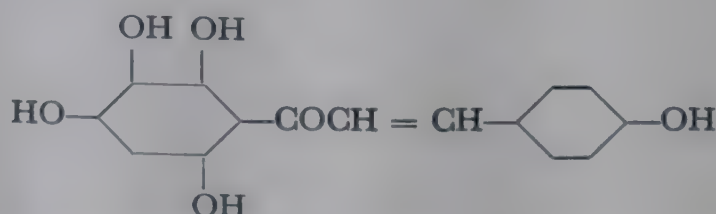


215°, is found as a glycoside in the flowers of the Eastern Asiatic tree, *Butea frondosa*, and gives them their colour. A second, colourless, isomeric substance, butin, also occurs in the flowers. It belongs to the class of hydroxyflavanones (see p. 559) (A. G. Perkin). Butein and butin are closely related. On ring closure (brought about, for example, by means of sulphuric acid), butein is converted into butin, and when the ring of the latter is ruptured (for example, with alkalis), butin is reconverted into butein:

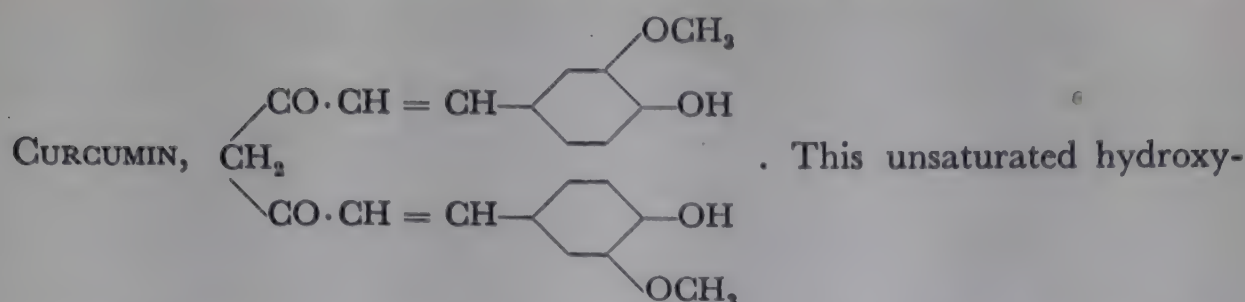


This reciprocal transformation of butein and butin is also believed to take place normally in the plant.

Safflower, the dried petals of the colour thistle (*Carthamus tinctorius*), which was formerly used for dyeing cotton and silk, contains the yellow pigment CARTHAMIN, a derivative of chalcone:



The pentamethyl ether of this compound has been synthesized and has been proved to be identical with the product obtained by methylating carthamin.



ketone is the colouring principle of curcuma (turmeric), i.e. the dye from the rhizomes of *Curcuma tinctoria*, which flourishes in the East. Curcumin dyes cotton directly to a yellow shade. It is one of the few natural substantive dyes for cotton. It melts at 178°. Curcumin still finds a limited use as a dye for silk, and is also used as an indicator (gives a brown colour with caustic alkalis, and a red coloration with boric acid).

The constitution of curcumin has been elucidated by the investigations of Milobędzka, Kostanecki, and Lampe, and has been verified by synthesis (Lampe).

CHAPTER 38

SIMPLE AROMATIC CARBOXYLIC ACIDS

Benzoic acid, $\text{C}_6\text{H}_5\text{COOH}$

The prototype of the aromatic carboxylic acids, *benzoic acid*, is present in various balsams (Tolu balsam, Peru balsam). As an ester it is an important constituent of gum benzoin (12–18 per cent). A compound of benzoic acid with glycine, *hippuric acid*, $\text{C}_6\text{H}_5\text{CONHCH}_2\text{COOH}$, is an excretory product of the animal organism. It occurs particularly in the urine of horses and cattle, from which it was formerly isolated. In birds, benzoic acid is conjugated with the amino-acid ornithine, to give ornithuric acid



Many methods are available for the artificial preparation of benzoic acid. It may be obtained:

1. By oxidation of various benzene derivatives with a side chain, e.g. toluene, ethylbenzene, benzyl alcohol, etc.:

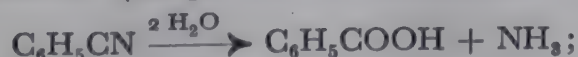


2. By the action of sodium on an equimolecular mixture of bromobenzene and chloroformic ester:



3. From bromobenzene, by converting it into phenylmagnesium bromide. The latter reacts with carbon dioxide in exactly the same way as the alkylmagnesium compounds (see pp. 192-1).

4. From benzonitrile (see p. 524) by hydrolysis with acids or alkalis:



5. By distillation of sodium benzenesulphonate with sodium formate:



Benzoic acid crystallizes in colourless leaflets or needles, which melt at 121° . It is readily soluble in alcohol and ether, but is difficultly soluble in water. It is one of the longest known of all organic acids. It was found as a sublimation product of gum benzoin even at the commencement of the XVIIth century. Its more thorough investigation was carried out by Liebig and Wöhler, who in their great work on the benzoyl radical (1832), also opened up the chemistry of the derivatives of benzoic acid. See below.

The acid is used to-day to a fairly considerable extent in the dyeing industry, e.g. in the synthesis of Aniline blue (see p. 614), and several anthraquinone dyes (q.v.). On account of its antiseptic properties it is used as a preservative for food. Various derivatives of benzoic acid are used in considerable quantities.

Derivatives of benzoic acid

METHYL BENZOATE, $C_6H_5COOCH_3$. The esterification of aromatic acids is carried out by the same methods as in the aliphatic series. Thus, methyl benzoate is obtained by boiling together benzoic acid, methyl alcohol and some sulphuric acid, or by the action of benzoyl chloride (q.v.) on methyl alcohol. The ester is a colourless liquid with a pleasant smell; it is used in perfumery (Niobe oil). It boils at 198° .

BENZOYL CHLORIDE, C_6H_5COCl (m.p. -1° , b.p. 198°), is made from benzoic acid and phosphorus pentachloride. It is an important reagent, being used particularly for introducing the benzoyl radical into compounds. The most common method of benzoylation is that due to Schotten-Baumann. The hydroxy-compound to be benzoylated is shaken with benzoyl chloride, in aqueous alkali solution. The benzoylated compound separates out, whilst excess of benzoyl chloride is converted into sodium benzoate and goes into solution:



Instead of alkali, anhydrous pyridine is now often used to retain hydrogen chloride.

Benzoyl chloride also reacts readily with amines giving benzoylamino compounds: $2 RNH_2 + ClCOC_6H_5 \longrightarrow RNHCOC_6H_5 + RNH_2, HCl$.

With diazomethane, diazoacetophenone, $C_6H_5COCHN_2$, is the chief product, and this is a convenient method of preparing aliphatic diazo-compounds.

BENZOIC ANHYDRIDE, $(C_6H_5CO)_2O$, m.p. 42° , is, like benzoyl chloride, a benzoylating agent. It is made from benzoyl chloride and sodium benzoate:



DIBENZOYL PEROXIDE, $(C_6H_5CO)_2O_2$, a diacyl derivative of hydrogen peroxide is formed by the action of benzoyl chloride on sodium peroxide:



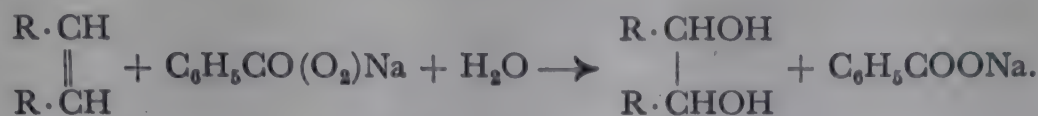
It is very stable, and forms colourless crystals, m.p. $106-8^{\circ}$. On account of its oxidizing and disinfecting properties it is occasionally used as an antiseptic.

Dibenzoyl peroxide reacts with sodium ethylate to give ethyl benzoate and sodium perbenzoate, $C_6H_5CO(O_2)Na$:



PERBENZOIC ACID melts at $41-43^{\circ}$, and explodes weakly on heating. It is an oxidizing agent, and as such it has gained a certain importance in syntheses, since

it is often possible by its aid to convert ethylene derivatives fairly smoothly into glycols:



DITHIOBENZOIC ACID, $\text{C}_6\text{H}_5\text{CSSH}$. This rather unstable, bluish red compound is formed by the action of carbon disulphide on phenylmagnesium salts. Its deep colour is remarkable. The $\text{C}=\text{S}$ group has strong chromophoric properties. The insoluble lead salt of dithiobenzoic acid is also purple-red in colour.

BENZAMIDE, $\text{C}_6\text{H}_5\text{CONH}_2$, is a colourless compound, which crystallizes well. It melts at 130° . It is prepared by the action of ammonia on ethyl benzoate or benzoyl chloride, i.e. by methods analogous to those employed for preparing the aliphatic amides (q.v.). A newer method of obtaining aromatic amides depends on the reaction between aromatic hydrocarbons and cyanates in the presence of aluminium chloride and hydrogen chloride. The reaction may possibly proceed as follows:

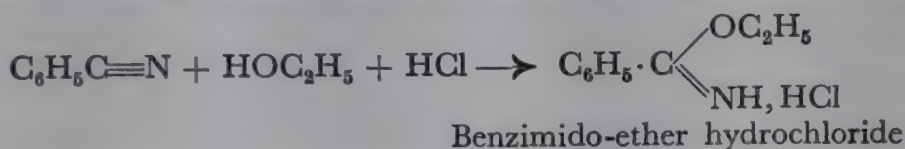


In its chemical reactions benzamide behaves in exactly the same manner as the aliphatic amides. When submitted to the Hofmann degradation it gives aniline.

Benzamide forms metallic compounds, such as sodium benzamide, which probably exists in the tautomeric forms $\text{C}_6\text{H}_5\text{C}(\text{ONa})=\text{NH}$ and $\text{C}_6\text{H}_5\text{CO} \cdot \text{NHNa}$.

BENZIMIDO-ETHER, $\text{C}_6\text{H}_5\text{C} \begin{array}{l} \nearrow \text{OC}_2\text{H}_5 \\ \searrow \text{NH} \end{array}$. The aromatic imido-ethers behave entirely in

the same manner as the corresponding compounds of the aliphatic series (see p. 224). They are best prepared by treating a mixture of a nitrile and alcohol with hydrogen chloride:

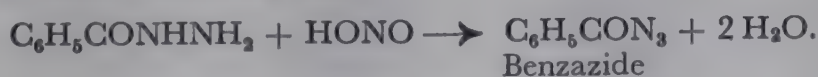


Silver benzamide reacts with alkyl iodides to give imido-ethers.

The free benzimido ethyl ether is a liquid with a pleasant smell, boiling at 219° . Its hydrochloride forms large prisms.

BENZOHYDRAZIDE, $\text{C}_6\text{H}_5\text{C} \begin{array}{l} \nearrow \text{O} \\ \searrow \text{NH} \cdot \text{NH}_2 \end{array}$, m.p. 112° , is prepared from ethyl benzoate and hydrazine.

Benzohydrazide is the starting point for the preparation of *benzazide*, into which it is converted by the action of nitrous acid:



The latter compound is converted by alkali into benzoic acid and hydrazoic acid. It was in this way that Curtius discovered hydrazoic acid (1890):



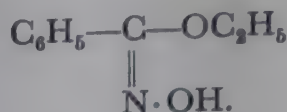
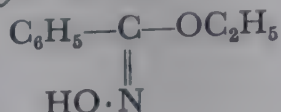
The aromatic acid azides are also of interest as intermediate compounds in the conversion of a carboxylic acid into an amine. On heating in alcoholic solution they undergo the Curtius rearrangement (see p. 130). Benzazide gives phenylurethan.

BENZOHYDROXAMIC ACID. The compound exists in one of the tautomeric forms indicated by the formulæ:



It is formed as a crystalline solid (m.p. 124°) by the action of hydroxylamine on the esters, chloride, and amide of benzoic acid. It has an acid reaction, and gives a red complex iron salt with ferric chloride.

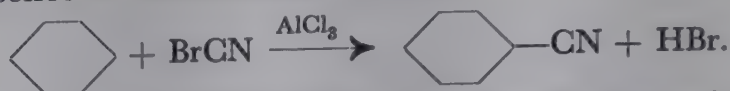
Alkyl ethers, the *alkyl-benzhydroxamic acids*, are derived from formula (b). They exist in two stereoisomeric forms, which, like the isomeric oximes of unsymmetrical ketones, are to be regarded as *syn*- and *anti*-forms:



Benzonitrile, phenyl cyanide, $\text{C}_6\text{H}_5\text{CN}$

In addition to the methods by which aliphatic nitriles are prepared, and which also hold for aromatic nitriles (e.g. removal of water from amides or aldoximes, isomerization of isonitriles, see p. 187), there are others peculiar to aromatic nitriles:

1. The action of cyanogen bromide on aromatic hydrocarbons and phenolic ethers in the presence of aluminium chloride:



2. Treatment of the diazonium salts with potassium cuprocyanide, $[\text{Cu}(\text{CN})_4]\text{K}_3$ (see p. 478).

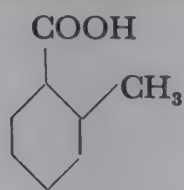
3. Distillation of the alkali salts of arylsulphonic acids with potassium cyanide or potassium ferrocyanide:



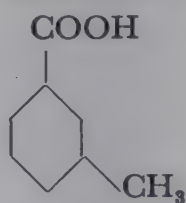
Benzonitrile is a colourless neutral liquid with a pleasant smell of bitter almonds. It boils at 191° . On treatment with sodium and boiling alcohol it is partly reduced to benzylamine, and partly hydrolysed to benzoic acid. Like the aliphatic nitriles, benzonitrile tends to form addition compounds and to enter into polymerization reactions. For example, cold, fuming sulphuric acid converts it into the trimolecular cyaphenine (= sym. triphenyltriazine; see Ch. 62).

Homologues of benzoic acid

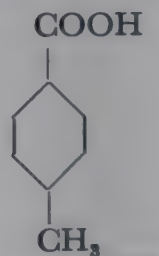
The three possible structurally isomeric *methylbenzoic acids*, or *toluic acids*:



m.p. 105°



m.p. 111°



m.p. 180°

can be prepared by the partial oxidation of the isomeric xylenes, or better from the corresponding toluidines, through the diazonium salts and nitriles.

There is no need to discuss the individual compounds. The fact that *o*-toluic acid has a dissociation constant about twice as great as that of its isomers, or of benzoic acid, is, however, noteworthy.

PHENYLACETIC ACID, $\text{C}_6\text{H}_5\text{CH}_2\text{COOH}$, which has the carboxyl group in the side chain, is best prepared from benzyl chloride, through the cyanide:

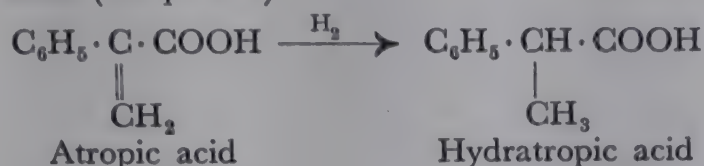


It melts at 76° , and distils at 265° . Its acidity is somewhat less than that of benzoic acid. The reactivity of the methylene group in phenylacetic acid should be noted; this is made use of in many syntheses (e.g. Pschorr's synthesis of phenanthrene).

In the organism, phenylacetic acid combines with glycine to give phenaceturic acid, $\text{C}_6\text{H}_5\text{CH}_2\text{CO}\cdot\text{NHCH}_2\text{COOH}$, in which form it is excreted.

Phenylacetic acid and its esters are used as perfumes for waxes and honey.

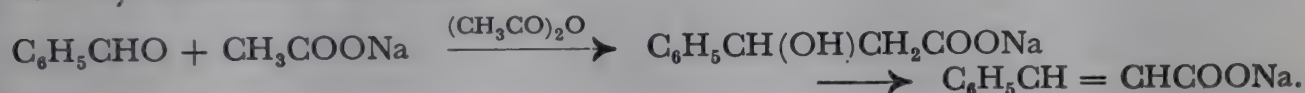
PHENYLMETHYLACETIC ACID, $\text{C}_6\text{H}_5\text{CH}(\text{CH}_3)\text{COOH}$, is also called *hydratropic acid*, because it can be obtained by the reduction of the unsaturated, naturally occurring atropic acid (see p. 527):



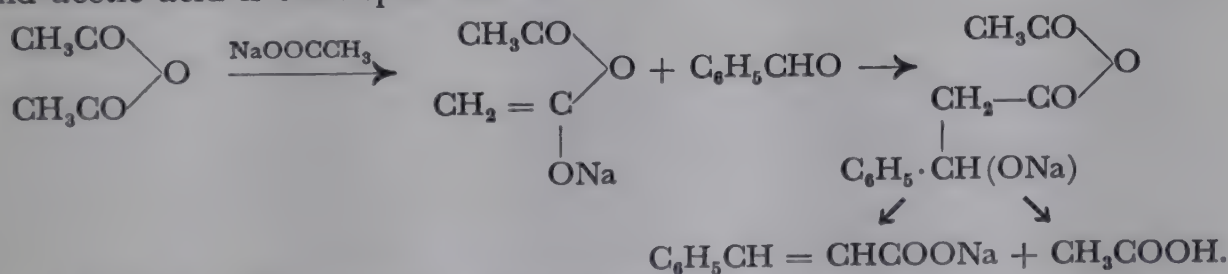
Unsaturated aromatic carboxylic acids

CINNAMIC ACID, $\text{C}_6\text{H}_5\text{CH}=\text{CHCOOH}$. This acid, partly in the free form, but chiefly as its esters, is contained in essential oils and resins, in Peru and Tolu balsams, and in coca leaves. Various good methods are known by which it may be prepared artificially:

1. It is obtained by Perkin's reaction by heating benzaldehyde with anhydrous sodium acetate and acetic anhydride, some drops of pyridine being added to act as a catalyst. The process probably takes place in two stages. First a β -hydroxy-acid is formed by an aldol condensation. This is then converted into cinnamic acid by elimination of water:

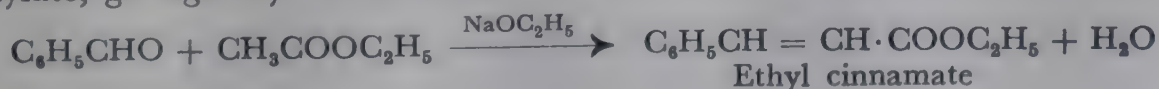


Kalnin and E. Müller suppose that in the Perkin synthesis, the acid anhydride acts in its enol form, which is reactive, and that the sodium acetate (which can be replaced by other substances, such as pyridine, triethylamine, etc.) favours this enolization, and also acts as an agent for removing acetic acid. According to this view the aldehyde adds on primarily to the enol form of the acid anhydride, and acetic acid is then split off:



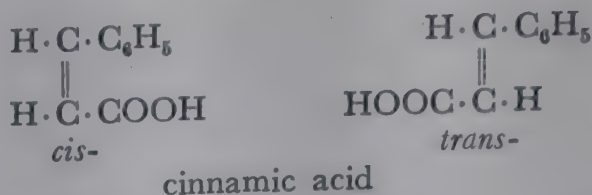
Actually, acid anhydrides dissolved in pyridine, show active H-atoms in the Zerewitinoff estimation, from which it can be concluded that they are enolized. In anisole, xylene, etc., the enolization is less.

2. Claisen condensed benzaldehyde and ethyl acetate by means of sodium ethylate, giving ethyl cinnamate:

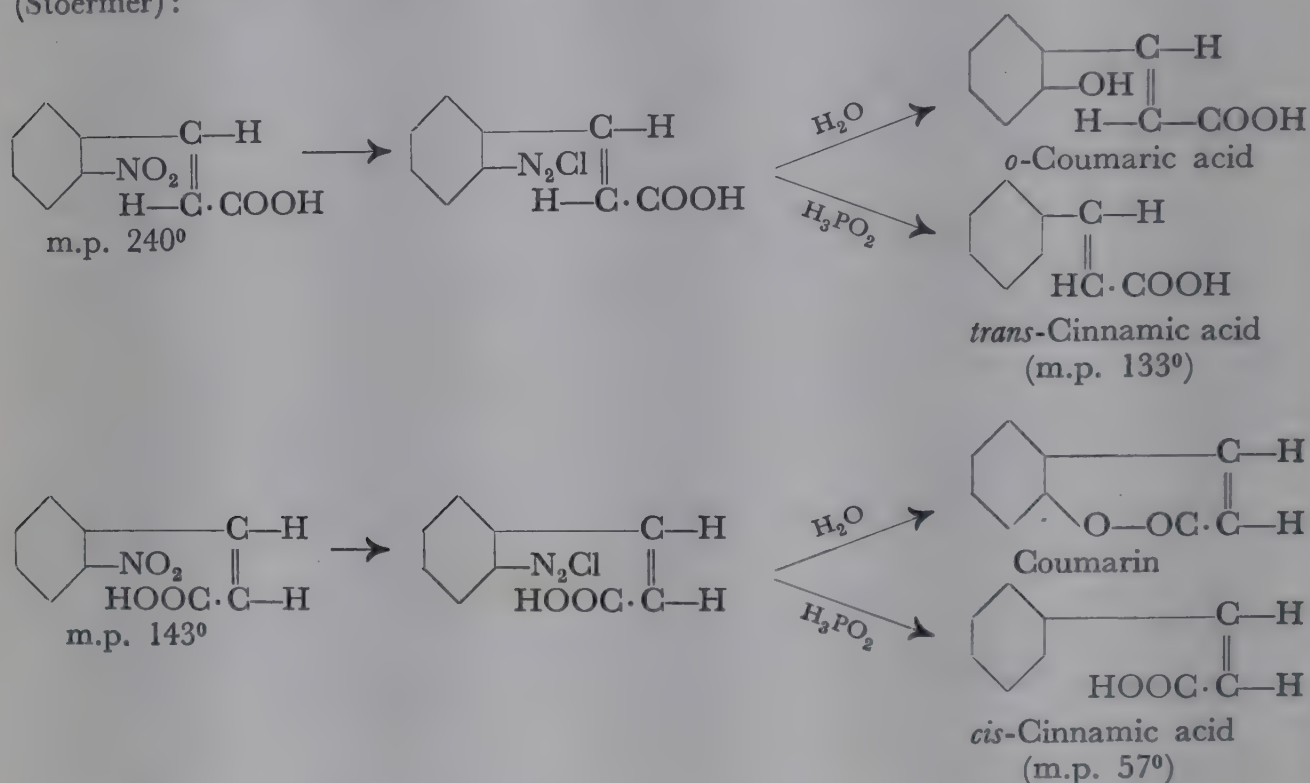


3. Technically, cinnamic acid is usually prepared by the oxidation of benzylidenacetone, $C_6H_5CH=CHCOCH_3$ (the condensation product of benzaldehyde and acetone) with hypochlorous acid.

Since it is an ethylenic derivative, cinnamic acid exists in a *cis*- and a *trans*-form:



The following is a proof of the configurations of the two cinnamic acids. There exist two *o*-nitrocinnamic acids, one of m.p. 240° , the other melting at 143° . The latter is labile, and is produced from the former by irradiation with ultra-violet light (see p. 283). The two nitro-acids give aminocinnamic acids on reduction. The diazo-compound of the one (obtained from the nitro-acid of m.p. 240°) gives on boiling *o*-coumaric acid, and on reduction with hypophosphorous acid, cinnamic acid of m.p. 133° . This cinnamic acid must have, like *o*-coumaric acid, the *trans*-configuration. The second aminocinnamic acid (from the nitro-acid of m.p. 143°) can be converted by analogous reactions into coumarin and cinnamic acid of m.p. 57° . The latter is, therefore, like coumarin, a *cis*-form (Stoermer):



The cinnamic acid which is obtained by methods 1–3 above is the *trans*-compound. It crystallizes in leaflets, which melt at 133° . It is only slightly soluble in cold water, and decomposes on distillation into styrene and carbon dioxide. Cinnamic acid has considerable technical interest. It has a limited use in medicine (tuberculosis), as have also its cresol and guaiacol esters. Its methyl, ethyl, and benzyl esters, however, are used as perfumes; it is also used for the preparation of bromostyrene, $C_6H_5CH=CHBr$ (hyacinth odour) and phenylacetaldehyde, important in perfumery.

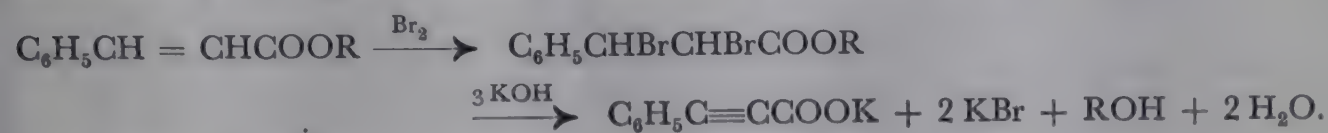
In addition to ordinary (or *trans*) cinnamic acid, there are three different *cis*-cinnamic acids, which are known as Liebermann's *allo*-cinnamic acid (m.p. 68°), Liebermann's *iso*-cinnamic acid (m.p. 57°), and Erlenmeyer's *iso*-cinnamic acid (m.p. $38\text{--}46^\circ$). As Biilmann proved, these are physical isomerides, polymorphic

forms, which can be very readily converted one into the other by seeding their melts. To prepare them use may be made of the mixture of acids obtained in the manufacture of cocaine by the hydrolysis of accessory cocaine alkaloids (see Ch. 67, 2).

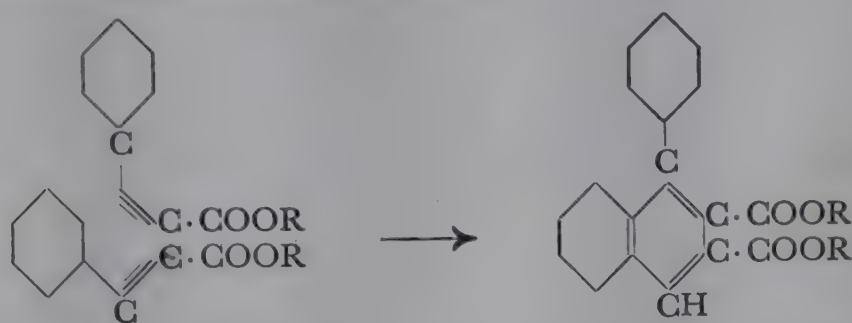
ATROPIC ACID, $C_6H_5C \cdot COOH$, see p. 549.



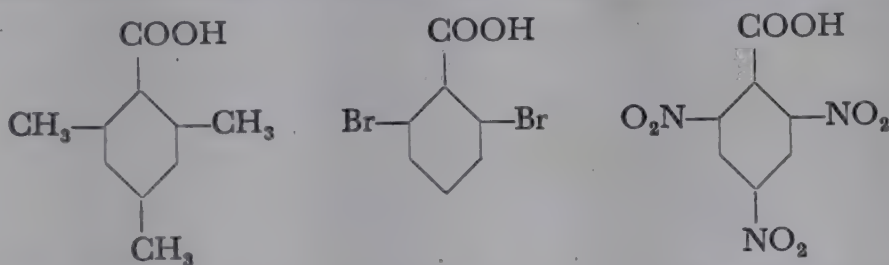
PHENYLPROPIOLIC ACID, $C_6H_5C \equiv CCOOH$, m.p. 136° , is formed from ethyl cinnamate by brominating it, and removing from the bromo-compound two molecules of hydrogen bromide by means of alcoholic potash:



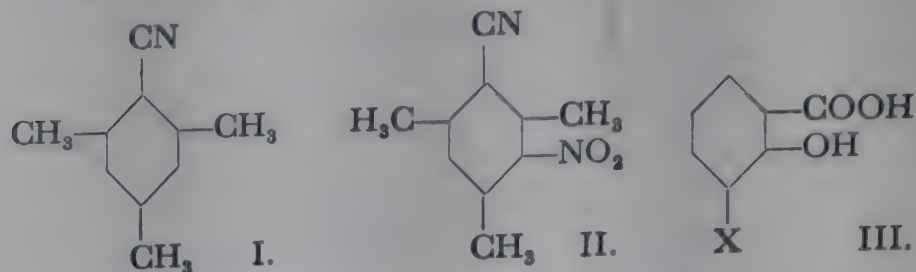
The ester of phenylpropionic acid can polymerize to a naphthalene derivative, 1-phenylnaphthalene-2:3-dicarboxylic ester:



In this compound the not uncommon phenomenon is observed that the ester group which stands between the phenyl radical and the other ester group, is very difficult to hydrolyse. In a corresponding manner the carboxyl groups of the acids:

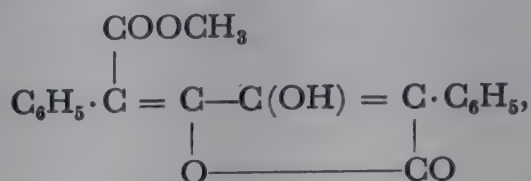


are difficultly esterified with alcohol and hydrogen chloride, and conversely, the esters are difficultly hydrolysed. It seems, therefore, that the carboxyl group is hindered with regard to its reactivity when it is in the *ortho*-position with respect to two substituents. This is often referred to as "steric hindrance", a term due to C. A. Bischoff and Victor Meyer, although the real cause of this lack of reactivity is not quite clear. The question is made still more complicated by the fact that the retardation of the process of esterification is limited in the case of the above acids to esterification with alcohol and acid, whilst the action of the silver salts of these acids on alkyl iodides proceeds quite smoothly. It appears that the *ortho*-substituent not only exerts an influence on the reactivity of the adjacent group because of the space it occupies, but also by affinity effects. Peculiar anomalies are therefore quite often encountered when dealing with steric hindrance. Thus, cyanide groups between two substituents (I), are usually very difficult to hydrolyse, but the presence of a *meta*-nitro-group can make the hydrolysis of the cyanide group much easier, although the latter stands between two substituents (II) (F. W. Kuster):

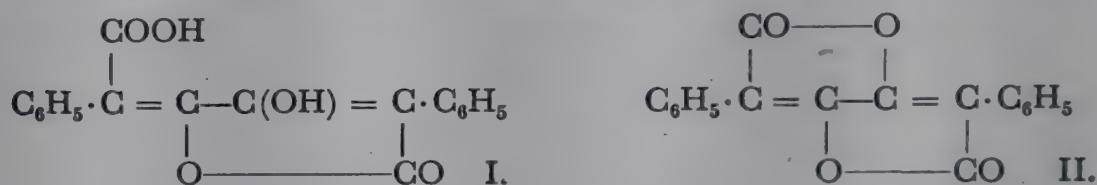


Another peculiar fact is that the phenolic OH in *ortho*-substituted salicylic acids (III) remains unchanged when treated with phosphorus pentachloride, but is replaced by chlorine when phosphorus trichloride is used (PCl_5 has a larger molecule).

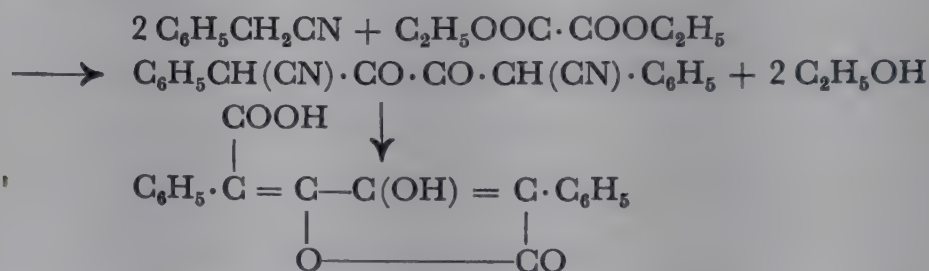
Vulpinic acid. A yellow pigment, *vulpinic acid*, is contained in species of lichens, particularly *Cetraria vulpina*. It crystallizes exceedingly well, and is poisonous. It possesses, as Spiegel and others have shown, the constitution:



and is thus the ester of a lactone-carboxylic acid. On hydrolysis with alkalis it is converted into pulvinic acid (I), and by heating into pulvinic acid lactone (II):



Pulvinic acid is readily synthesized by the condensation of benzyl cyanide with oxalic ester, and hydrolysing the dinitrile produced:



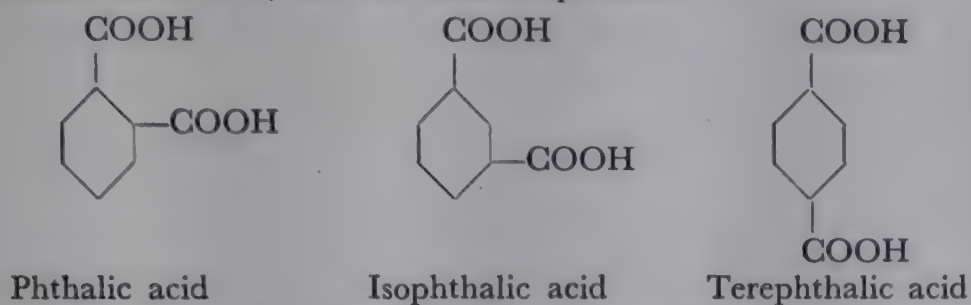
Pinastric acid, which occurs with vulpinic acid in *Cetraria pinastri* and *C. juniperina* is a *p*-methoxy-derivative of vulpinic acid.

(For pulvinic acid derivatives, see also p. 580.)

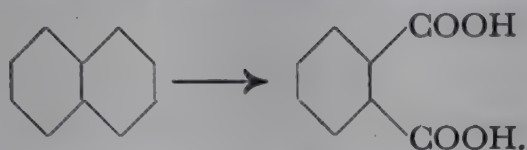
CHAPTER 39

POLYBASIC AROMATIC CARBOXYLIC ACIDS

PHTHALIC ACID. Of the three dicarboxylic acids of benzene, the *ortho*-compound, phthalic acid, is by far the most important:



It was discovered by Laurent (1836), who prepared it by oxidation of 1 : 2 : 3 : 4-tetrachloro-naphthalene with nitric acid. Later the Badische Anilin- und Sodafabrik developed a technically important process, which was based on a chance observation and consists in the oxidation of naphthalene with fuming sulphuric acid in the presence of a mercury salt as a catalyst:



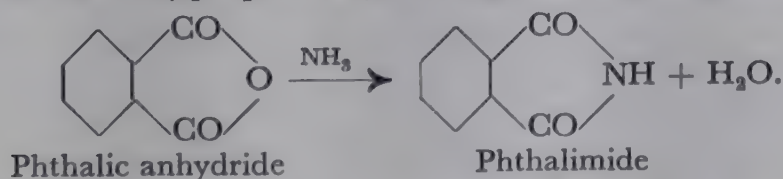
The compound has been prepared in this way for some decades. In more recent years the direct oxidation of naphthalene by atmospheric oxygen has been successfully carried out. In the presence of contact substances, such as molybdenum oxide, or vanadium pentoxide it proceeds smoothly and has become the most important technical synthesis of phthalic acid (C. E. Andrens, Wohl).

Phthalic acid melts at 196–199°, with frothing. It forms neutral and acid salts. It is only slightly soluble in water.

On heating, or when submitted to the action of dehydrating agents, phthalic acid is very readily converted into *phthalic anhydride*. The above-mentioned technical processes of manufacturing phthalic acid therefore yield chiefly the anhydride directly. It crystallizes in dazzling white, long needles which melt at 128°.

Phthalic anhydride is an exceedingly important compound technically. It is used in the synthesis of many dyes of the rhodamine and fluorescein series, vat dyes, phenolphthalein, etc. Indigo is prepared synthetically from phthalic anhydride through phthalimide and anthranilic acid (see p. 534 and p. 571).

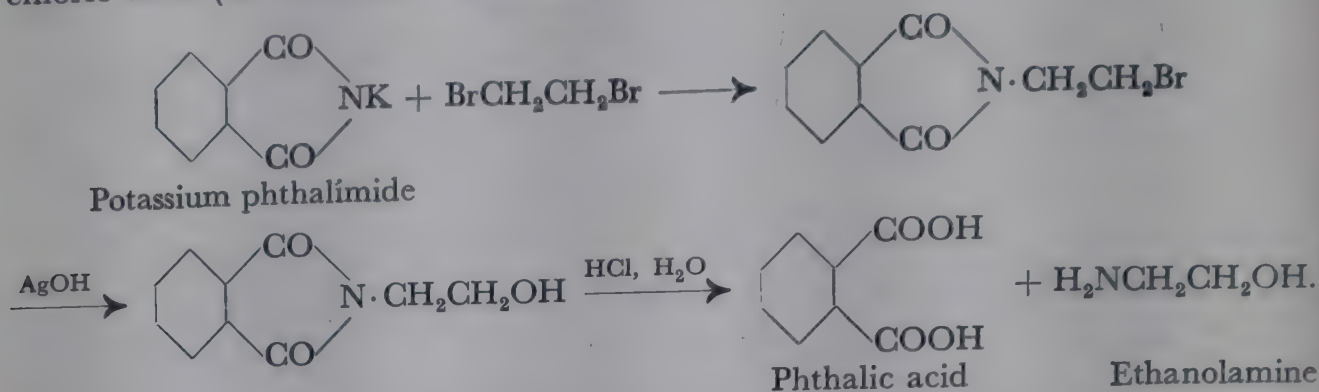
PHTHALIMIDE is easily prepared by heating phthalic anhydride with ammonia:



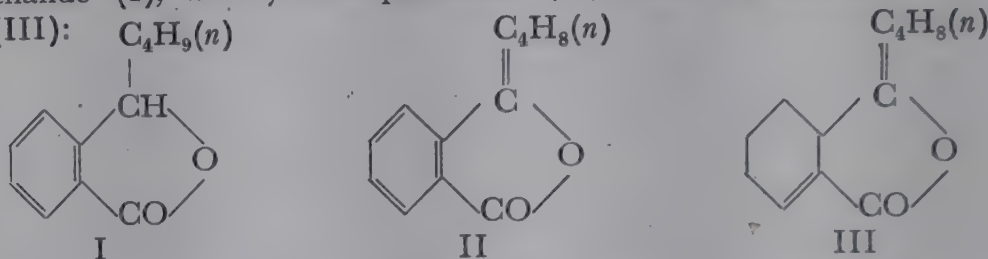
Its importance is due partly to the fact that it is easily converted into anthranilic acid (see p. 534) by the Hofmann degradation of acid amides (anthranilic acid is the starting point in the manufacture of indigo) and partly to the reactions of its potassium salt, which was used very successfully by Gabriel for the synthesis of aliphatic amines.

For example, if it is desired to prepare ethanolamine, $\text{H}_2\text{NCH}_2\text{CH}_2\text{OH}$,

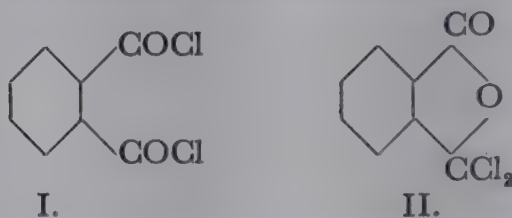
1 gm-mol. of potassium phthalimide is made to react with 1 gm-mol. of ethylene dibromide. Bromoethyl-phthalimide is thus produced. The bromine atom in this is replaced by hydroxyl in the usual way. It is then only necessary to eliminate the phthalic acid radical, which can be done by heating with concentrated hydrochloric acid (or concentrated alkali):



Phthalic acid has been found in the leaves and the seed of *Papaver somniferum* L. (poppy). The root oil of *Levisticum officinalis* Koch (lovage) contains among others, phthalides, namely *n*-butyl-phthalide (I), *n*-butylidene-phthalide (II), and Δ^2 -tetrahydro-*n*-butylidene-phthalide (III):

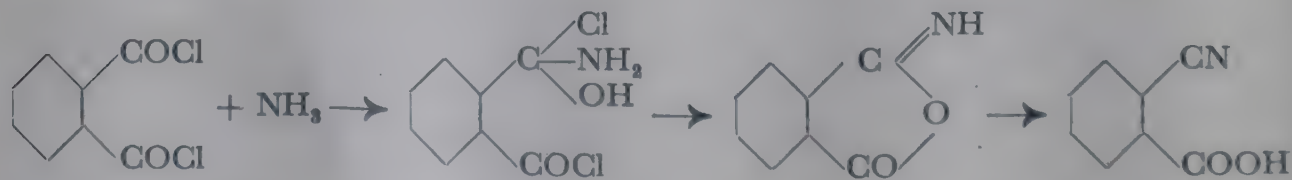


PHTHALYL CHLORIDE. Ordinary phthalyl chloride, prepared from phthalic acid and phosphorus pentachloride, has the symmetrical formula (I). It melts at 16°.



It readily isomerizes on treatment with aluminium chloride into the unsymmetrical form (II) (Ott), which melts at 88–89°, and is not very reactive. On heating, the unsymmetrical form, “isophthalyl chloride”, is reconverted into the symmetrical form.

When phthalyl chloride reacts with phenols and aluminium chloride, derivatives of the unsymmetrical form are always obtained, because the phthalyl chloride first isomerizes to the *iso*-form under the influence of the aluminium chloride. However, there are also other reactions, e.g. the action of ammonia, where the normal chloride apparently gives derivatives of the *iso*-form. Their formation is readily explained in the following way:

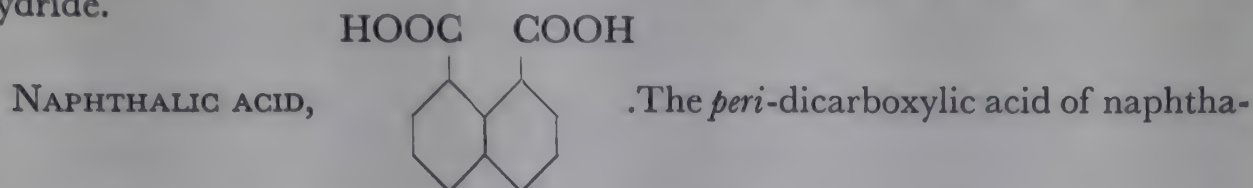


ISOPHTHALIC ACID (formula, see above) is obtained by oxidizing *m*-xylene with potassium permanganate. It melts at 348°. It does not form an anhydride, but

POLYBASIC AROMATIC CARBOXYLIC ACIDS

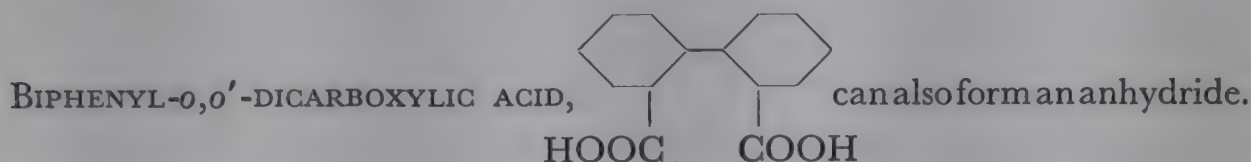
sublimes without decomposition. It is even more difficultly soluble in water than phthalic acid. It has no technical importance.

TEREPHTHALIC ACID (formula, see above), can be obtained by oxidizing *p*-toluic acid. It sublimes at about 300° without melting. It does not form an anhydride.

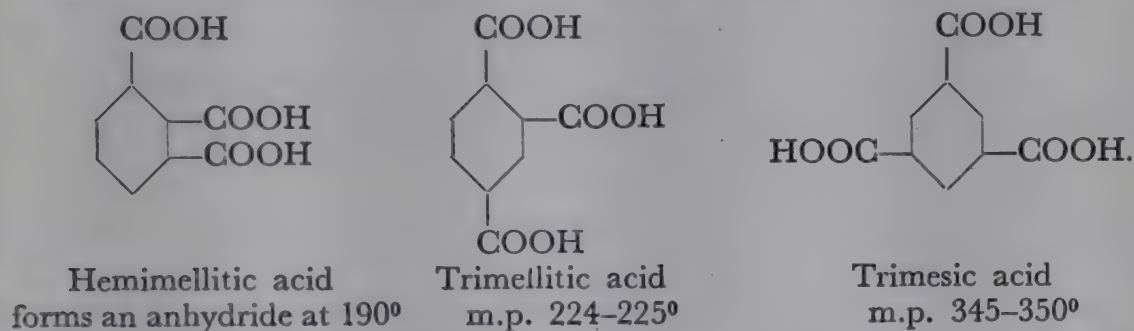


lene shows some similarities to phthalic acid. Like the latter it easily forms an internal anhydride, which enters into most of the reactions of phthalic anhydride. The analogy between the *ortho*-position in the benzene nucleus, and the *peri*-position in the naphthalene molecule, which has already been referred to, is thus further brought out in the dicarboxylic acids.

Naphthalic acid melts at 140–150°, and its anhydride at 274°. It is formed by the oxidation of acenaphthene (see p. 409).

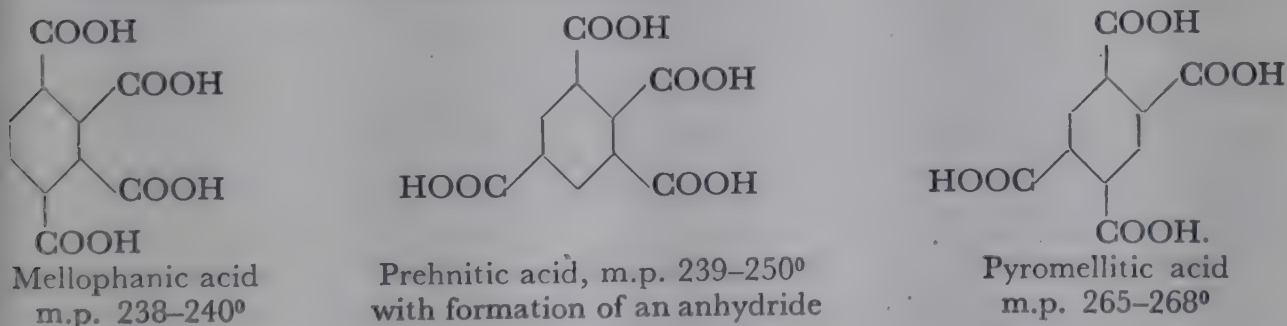


The three BENZENETRICARBOXYLIC ACIDS have the names:



They were first discovered in the course of investigations by A. von Baeyer on mellitic acid, from which they are produced by various decomposition reactions. They can be prepared by the oxidation of the isomeric trimethylbenzenes, but hemimellitic acid is most conveniently obtained from acenaphthene, which, on oxidative degradation, gives first naphthalic acid (q.v.), and then benzene-1:2:3-tricarboxylic acid.

TETRACARBOXYLIC ACIDS OF BENZENE:

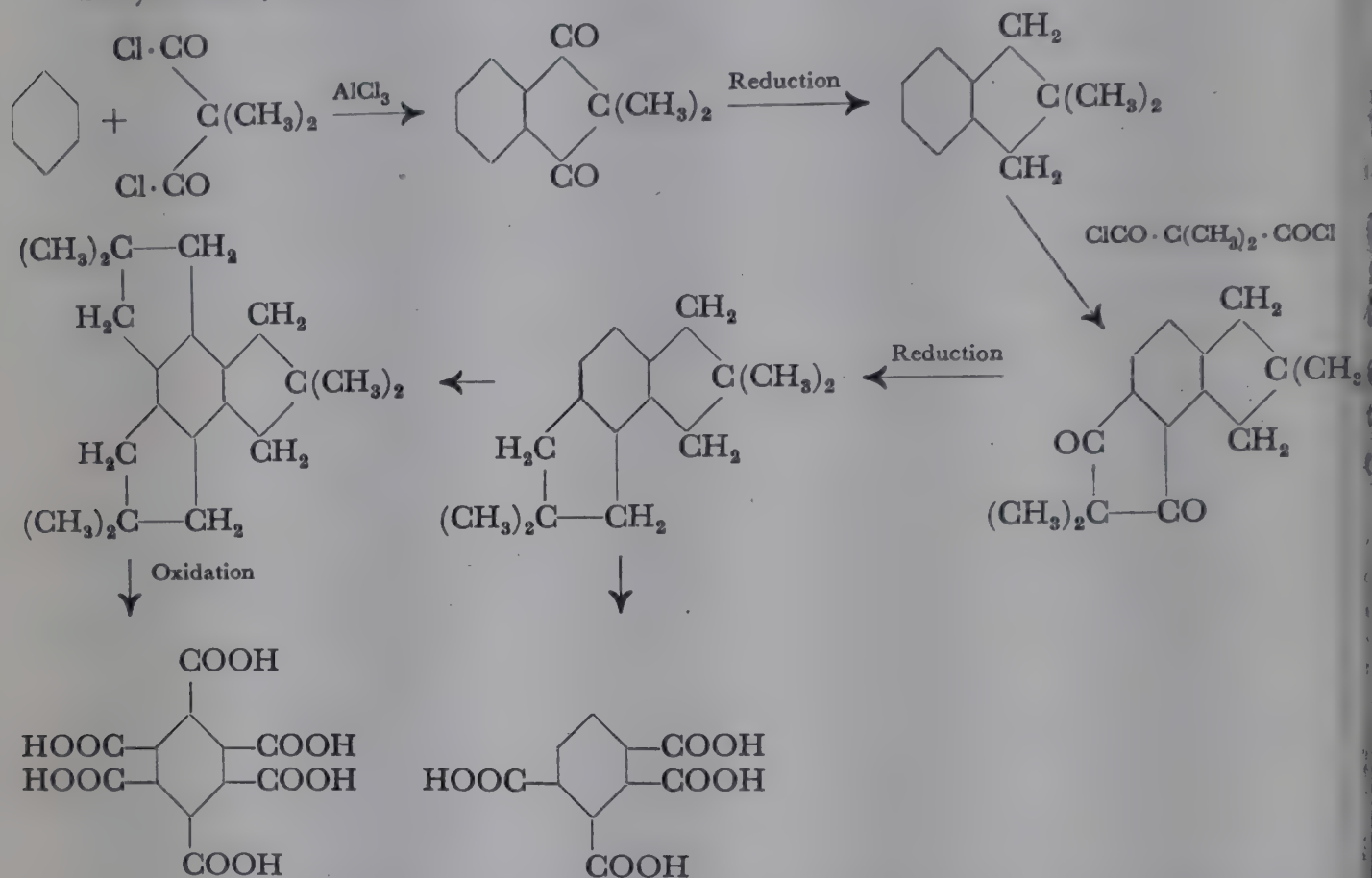


BENZENEPENTACARBOXYLIC ACID is also known; m.p. 238° (anhydrous).

MELLITIC ACID (benzenehexacarboxylic acid). The most important of the polycarboxylic acids of benzene is mellitic acid, of which the aluminium salt,

$\text{C}_{12}\text{O}_{12}\text{Al}_2 \cdot 18 \text{H}_2\text{O}$, occurs naturally as the mineral honeystone. Honeystone is found particularly in coal deposits. It crystallizes in square prisms.

Mellitic acid can be prepared by the oxidation of benzene derivatives with six side chains, e.g. from hexamethylbenzene (see p. 394), which is itself obtained from dimethylacetylene by polymerization. It is more conveniently prepared by a method due to M. Freund, which starts with benzene and dimethylmalonyl chloride, and, by systematic condensations and reductions, leads, by way of cyclic ketones and polycyclic hydrocarbons, to a hexasubstituted benzene derivative, which gives, on oxidation, mellitic acid. By appropriate changes the synthesis may also be used for the preparation of mellophanic acid, benzenepentacarboxylic acid, etc.:



The best method for the preparation of mellitic acid is the oxidation of graphite, charcoal, or amorphous carbon with nitric acid, preferably with the addition of some vanadic acid or silver nitrate as the so-called catalyst. A yellow amorphous substance, *graphitic acid*, occurs as an intermediate product. It appears to be a complex adsorption system of various degradation products of graphite on unchanged graphite.

The fact that benzenhexacarboxylic acid was obtained from carbon led to the conclusion that in the latter the individual carbon atoms were arranged in rings of six atoms. This was long before this view was confirmed by X-ray diffraction methods.

Mellitic acid is readily soluble in water and alcohol. It melts in a sealed capillary at $286\text{--}288^\circ$, and decomposes on distillation into carbon dioxide and pyromellitic anhydride. It is readily reduced by sodium amalgam to hexahydro-mellitic acid.

CHAPTER 40

CHLORO-, NITRO-, AND AMINO-DERIVATIVES OF AROMATIC CARBOXYLIC ACIDS

Chlorobenzoic acids. The chlorination of benzoic acid, in the presence of ferric chloride, leads to the formation of *m*-chlorobenzoic acid, as would be expected from the fact that the carboxyl group is a *meta*-directing substituent. At the same time, however, more highly chlorinated acids are formed, which are difficult to separate.

ortho- and *para*-Chlorobenzoic acids are most suitably prepared from the corresponding amino-acids via the diazonium salts. The oxidation of the isomeric chlorotoluenes may also be advantageously used.

All three chlorobenzoic acids crystallize well. The melting point of the *o*-compound is 138°, of the *m*-compound, 153°, and of the *p*-compound, 234°. The substitution in benzoic acid of the negative halogen atoms strengthens the acidic character of the substance, as the table of dissociation constants below shows.

Nitrobenzoic acids. The nitration of benzoic acid gives chiefly the *meta*-compound, together with about 20 % of the *ortho*- and very little (2 %) of the *para*-isomeride. The last two acids are prepared from *o*- and *p*-nitrotoluene by oxidation.

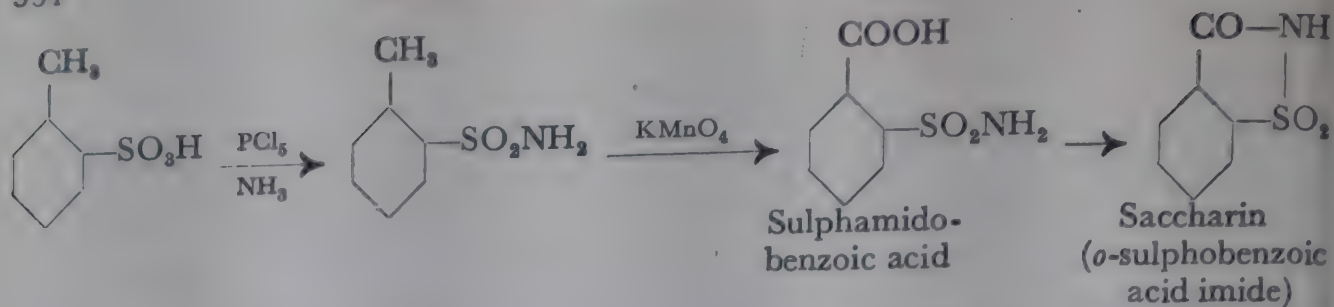
ortho-Nitrobenzoic acid tastes sweet. It melts at 148°. The *m*-acid melts at 141°, and the *p*-compound at 240°. *p*-Nitrobenzoic acid esters (dodecyl ester, *isohexyl* ester) are effective against pneumococcal infections. The nitrobenzoic acids, too, are stronger acids than benzoic acid.

	Dissociation const. K		Dissociation const. K
Benzoic acid	0.006	—	
<i>o</i> -Chlorobenzoic acid . . .	0.132	<i>o</i> -Nitrobenzoic acid. . . .	0.616
<i>m</i> - " "	0.0155	<i>m</i> - " "	0.0345
<i>p</i> - " "	0.0093	<i>p</i> - " "	0.0396

In the case of *o*-, *m*-, and *p*-fluoro-, chloro-, bromo-, and iodobenzoic acids, the four *ortho*-isomerides show almost exactly the same dissociation constants, as do also the *m*-isomerides and the *p*-isomerides, amongst themselves.

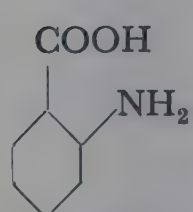
SACCHARIN.¹ This important substance, of which the sweetness exceeds that of cane sugar about five hundred times, is a derivative of *o*-sulphobenzoic acid. It was discovered by Remsen and Fahlberg in 1879. To prepare saccharin toluene is sulphonated, whereby *p*- and *o*-toluenesulphonic acids are obtained together. The latter is converted into the chloride, for which another more recent method of preparation consists in the direct action of chlorosulphonic acid on toluene. The chloride is then transformed into the amide, and this is oxidized with potassium permanganate to sulphamidobenzoic acid (m.p. 153–155°) which, even on evaporating the solution, anhydridizes forming *o*-sulphobenzoic acid imide, or saccharin:

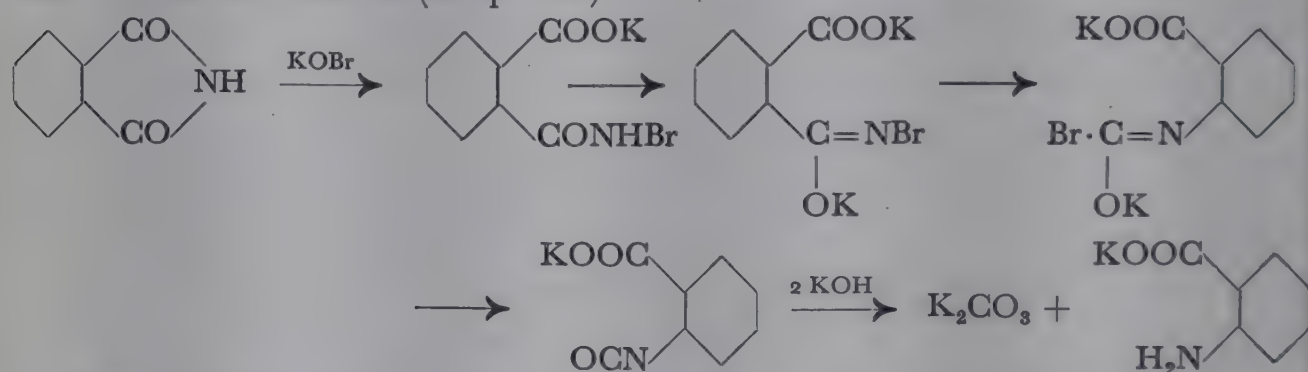
¹ See OSCAR BEYER, *Handbuch der Saccharinfabrikation*, Zürich, (1923).



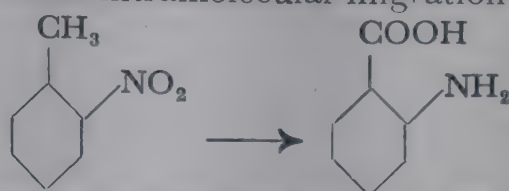
Saccharin forms colourless crystals, difficultly soluble in water, which melt at 220°. On boiling with water, it is slowly converted into *o*-sulphamidobenzoic acid, which does not taste sweet. It forms metal salts, of which those of the alkali metals are readily soluble in water. The sodium compound, $\text{C}_6\text{H}_4 \begin{smallmatrix} \text{CO} \\ \text{SO}_2 \end{smallmatrix} \text{N} \cdot \text{Na}$, which crystallizes very well, occurs in commerce under the name "crystallose".

Aminobenzoic acids.

 1. ANTHRANILIC ACID. The most important of the aminobenzoic acids, anthranilic acid, was discovered in 1841 by Fritzsche as a degradation product of indigo when treated with alkali. As the starting material for the preparation of indigo it is made commercially in large quantities. A convenient method of preparing it is the degradation of phthalimide with chlorine or bromine and alkali. Phthalamidic acid, $\text{C}_6\text{H}_4 \begin{smallmatrix} \text{COOH} \\ \text{CONH}_2 \end{smallmatrix}$, is an intermediate product. The bromine and caustic alkali convert it into anthranilic acid through the usual intermediate stages, as in the case of other acid amides (see p. 130):

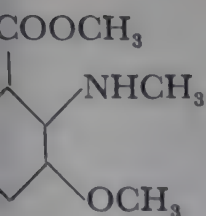


The numerous other known methods by which anthranilic acid can be formed cannot compete with this as a technical method of preparation. Anthranilic acid is obtained, though not in quantitative yield, by boiling *o*-nitrotoluene with alkali, through a peculiar intramolecular migration of hydrogen and oxygen:



Anthranilic acid crystallizes in white leaflets, m.p. 145°. It is moderately soluble in water, tastes sweet, and its solution shows a blue fluorescence. On distillation it decomposes into aniline and carbon dioxide.

In addition to the preparation of indigo, anthranilic acid is used in the synthesis of azo-dyes, thiosalicylic acid (see p. 574), and *methyl anthranilate*. The last occurs also naturally in essential oils, (Neroli, Jasmine oil), and is used in perfumery on account of its smell which is reminiscent of orange blossoms (m.p. 24°; b.p. 135° (15 mm)). N-Methylanthranilic methyl ester (m.p. 19°) has been detected in mandarine oil.



In the ranunculus *Nigella damascena* as well as in *Nigella aristata* the anthranilic acid derivative *damascenin* is found (Schneider). It is a methoxy-derivative of N-methylantranilic acid methyl ester, constituted as shown alongside. The compound melts at 24–26°, shows a blue fluorescence in solution, and has a narcotic effect.

2. *m*-AMINO BENZOIC ACID, prepared from *m*-nitrobenzoic acid by reduction, is used in the synthesis of azo-dyes (m.p. 174°).

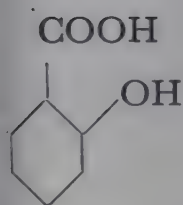
3. *p*-AMINO BENZOIC ACID is of particular interest in connection with the preparation of substances which act as local anæsthetics. Its ethyl ester, $\text{H}_2\text{N}-\text{C}_6\text{H}_4-\text{COOC}_2\text{H}_5$, is *anaesthesin*, or benzocaine (m.p. 90–91°), its propyl ester is *propaesin*, the hydrochloride of the diethylaminoethyl ester is *novocaine*, $\text{H}_2\text{N}-\text{C}_6\text{H}_4-\text{COOCH}_2\text{CH}_2\text{N}(\text{C}_2\text{H}_5)_2\text{HCl}$ (see also p. 248).

p-Aminobenzoic acid is prepared from *p*-nitrobenzoic acid by reduction, or from N-acetyl-*p*-toluidine by oxidation to *p*-acetylaminobenzoic acid and subsequent hydrolysis of the acetyl radical. It melts at 186–187°. It has been found to be a physiologically active substance, which is capable of curing a greyness in the hair of rats resulting from their diet. It is essential for the growth of chickens (Ansbacher), and belongs to the group of B-vitamins (see Ch. 56). *p*-Aminobenzoic acid occurs in yeast, in part as a constituent of peptides, which contain several (6–11) glutamic acid groups, and it also takes part in the structure of the vitamin folic acid (= pteroylglutamic acid).

CHAPTER 41. AROMATIC HYDROXY-ACIDS

A. Hydroxy-acids with a phenolic nature

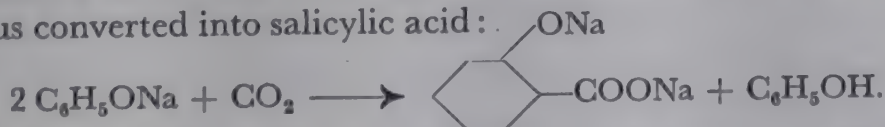
1. Monohydroxycarboxylic acids.



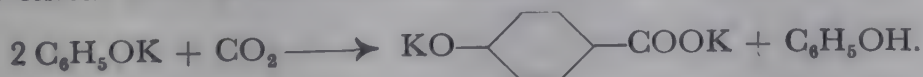
SALICYLIC ACID. Of the three position-isomeric monohydroxybenzoic acids, salicylic acid, the *ortho*-compound, is the most important. It is found in *Gaultheria procumbens* L. as a glycoside of methyl salicylate, methyl salicylate primveroside, which is called monotropitide (from *Monotropa hypopitys*, in which it was discovered).

Free salicylic acid has been detected in Senega root.

Salicylic acid, discovered by Piria in 1838, has been prepared synthetically since 1874. The older synthesis of the acid was due to Kolbe. In this process, dry sodium phenate is heated in a stream of carbon dioxide to 180–200°. Half of the phenol is thus converted into salicylic acid:



The reaction proceeds somewhat differently if potassium phenate is used instead of sodium phenate. Between 100° and 150°, dipotassium salicylate is formed in a similar way, but at higher temperatures this is converted to a greater and greater extent into the salt of the isomeric *p*-hydroxybenzoic acid:

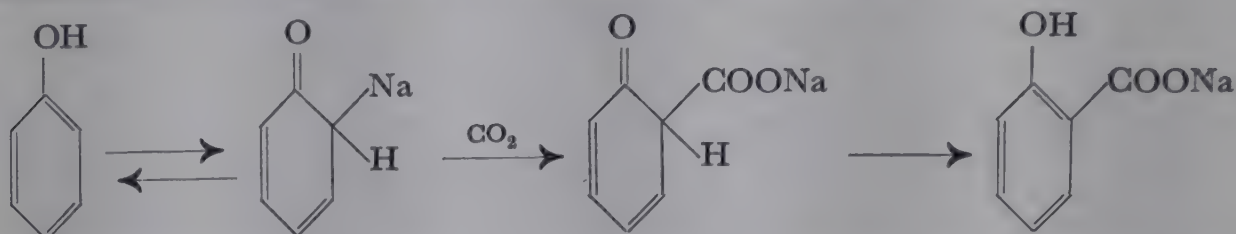


The isomerization is complete above 200°.

Kolbe's synthesis of salicylic acid was later considerably improved by R. Schmitt. In this case carbon dioxide is allowed to react with dry sodium phenate under pressure in an autoclave first at ordinary temperatures, and is afterwards heated to 120–140°. According to Schmitt's view the first phase of the reaction consists in the formation of sodium phenyl carbonate, which isomerizes on heating under pressure, giving sodium salicylate:

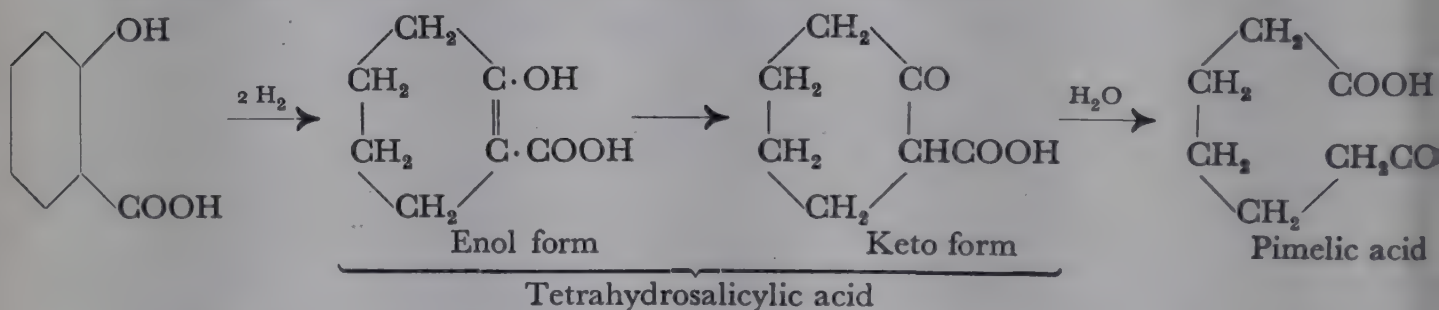


According to another view (Tijmstra), the sodium phenate adds on carbon dioxide direct, so that the reaction product is sodium phenate *o*-carboxylic acid. A third interpretation assumes the reaction to proceed through sodium *cyclohexadienone*, the tautomeric form of sodium phenate (H. Gilman):

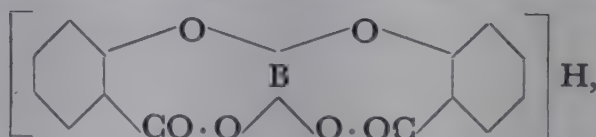


The advantage of Schmitt's process over the older method of Kolbe lies in the fact that by it *all* the phenol is converted into salicylate.

Salicylic acid crystallizes in colourless needles, melting at 156–157°. It is fairly soluble in water, and easily in alcohol and ether. It tastes both acid and sweet, and gives a violet coloration with ferric chloride. With reducing agents it is easily broken down into pimelic acid. Tetrahydrosalicylic acid is an intermediate compound in this reaction. It exists in the keto form as a β -ketonic acid, and as such undergoes "acid hydrolysis" to pimelic acid:



Salicylic acid combines with boric acid to give *borosalicylic acid*:



which can be resolved into optically active forms (Böeseken). This very interesting fact shows that the arrangement of the substituents about the coordinately tetra-valent boron is tetrahedral, since compounds of the above type could only show enantiomorphism with such a steric structure.

On account of its antiseptic properties salicylic acid is widely used as a preservative for fruit, foodstuffs, proteins, wine etc. It is used in medicine as an antiseptic and disinfectant, and, taken internally, as a specific against rheu-

matism of the joints. Its acetyl derivative, *aspirin*, $\text{C}_6\text{H}_4 \begin{matrix} \text{OCOCH}_3 \\ \text{COOH} \end{matrix}$ (m.p. 135°), is largely used on account of its antipyretic, antineuralgic, and analgesic

properties. The phenyl ester of salicylic acid, $\text{C}_6\text{H}_4\begin{matrix} \text{OH} \\ \text{COOC}_6\text{H}_5 \end{matrix}$ (m.p. 42–43°), is the well-known antiseptic, *salol*, which is obtained by fusing together salicylic acid, phenol, and phosphorus oxychloride.

Salicylic acid is used in the dyeing industry especially as a coupling component in the synthesis of azo-dyes. It endows these with the power of attaching themselves to mordants (see page 491).

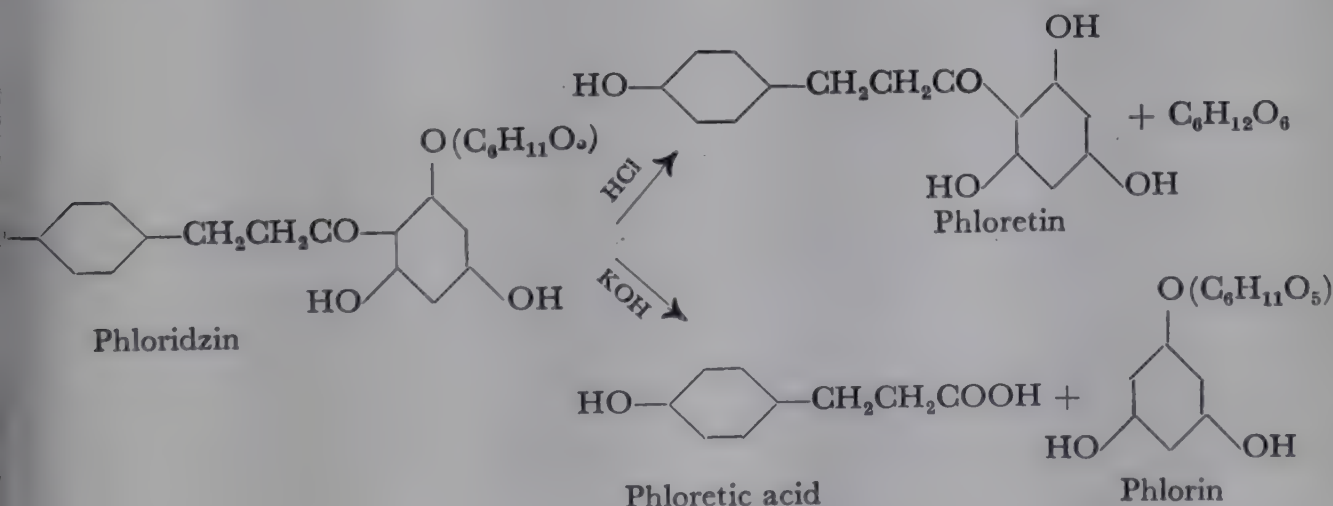
METHYL SALICYLATE, the chief constituent of oil of wintergreen, occurs as a glycoside in different plants (see p. 535). It is an important perfume, and boils at 222°.

m-HYDROXYBENZOIC ACID crystallizes in needles or leaflets, melts at 188°, and gives no coloration with ferric chloride. It is made technically from *m*-sulphobenzoic acid by fusion with alkali. It has no antiseptic properties, but has a certain use in the production of azo-dyes.

p-HYDROXYBENZOIC ACID. The preparation of this compound from potassium phenate has been mentioned on p. 535. It melts at 213°. Ferric chloride gives an amorphous, yellow precipitate with an aqueous solution of the acid. *p*-Hydroxybenzoic acid and its esters have bactericidal properties.

ANISIC ACID, $\text{CH}_3\text{O}-\text{C}_6\text{H}_4-\text{COOH}$, the methyl ether of *p*-hydroxybenzoic acid, is produced by the oxidation of anethole. It melts at 184°. Anisoyl derivatives often serve instead of benzoyl derivatives for the characterization of phenols, amines, etc.

PHLORETIC ACID, $\text{HO}-\text{C}_6\text{H}_4-\text{CH}_2\text{CH}_2\text{COOH}$, is formed by the hydrolysis of the glycoside *phloridzin* (or *phlorrhizin*), which is contained in the bark of the root and stem of apple, pear, and plum trees. If the glycoside is boiled with dilute mineral acids, only the sugar radical is hydrolysed and a polyhydroxy-ketone, *phlorethin*, is produced. Hot alkalis, however, decompose phlorethin and phloridzin further into phloretic acid and phloroglucinol or phloroglucinol glycoside (*phlorin*):

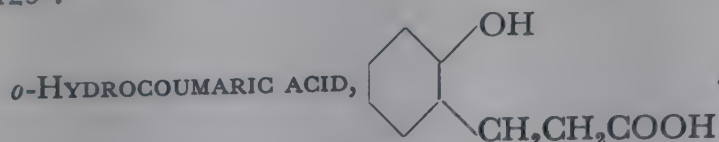


The constitution of phlorethin has been verified by synthesis (condensation of phloroglucinol and the nitrile of phloretic acid (*p*-hydrocoumaronitrile) by

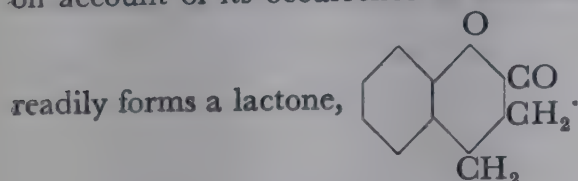
means of hydrogen chloride). Also the glycoside phlorrhicin has been produced synthetically.

The glycoside phloridzin is of physiological interest since it induces glycosuria in animals.

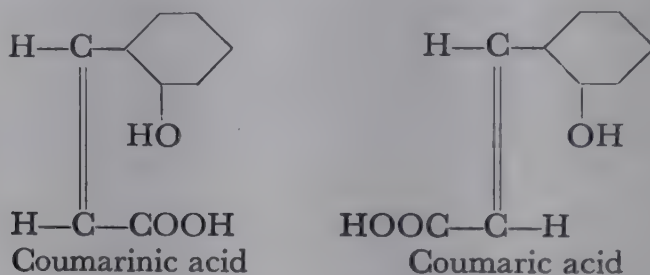
Phloretic acid, or *p*-hydrocoumaric acid, is moreover contained in human urine, and is produced in the decay of flesh as a degradation product of tyrosine (see p. 287); m.p. 128–129°.



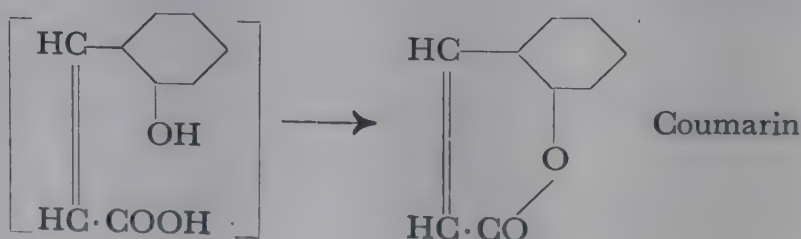
on account of its occurrence in *Melilotus officinalis* (melilot trefoil). It melts at 83°, and



o-HYDROXYCINNAMIC ACIDS. Like cinnamic acid itself (see p. 525) its *ortho*-hydroxy-derivative exists in two *cis-trans* isomerides, of which the *cis*-form is known as *coumarinic acid* and the *trans*-compound as *o*-*coumaric acid*:

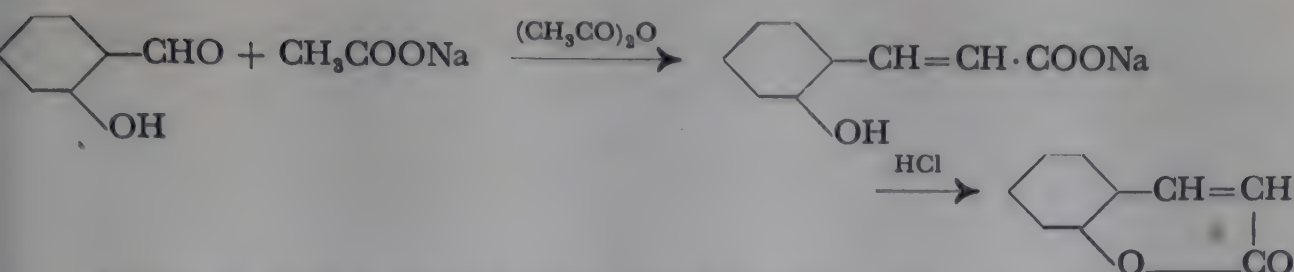


In the free state, however, only *o*-coumaric acid is stable. Coumarinic acid is known in the form of salts. When attempts are made to isolate the free acid from them, it immediately loses one molecule of water and is converted into the lactone, *coumarin*:



This extremely ready formation of an anhydride by coumarinic acid is the reason why it is given the *cis*-configuration, and coumaric acid the *trans*-configuration. The isomeric coumarinic-coumaric acids are among the longest known and best investigated examples of stereoisomeric ethylenic compounds. Coumarin is contained, apparently in glycosidic form, in many plants, particularly the Tonquin bean and woodruff. That is why the smell of coumarin first becomes apparent during the drying of the plants as in the case of hay, its formation being accompanied by a hydrolysis of the glycoside.

Coumarin is prepared technically by Perkin's synthesis from salicylaldehyde, sodium acetate, and acetic anhydride:



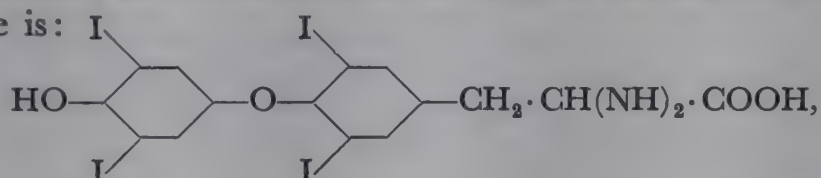
Coumarin forms colourless crystals, with a pleasant smell (resembling woodruff or hay). It melts at 67° . Solutions of the alkali-metal salts of coumarinic acid are yellow.

Coumarin has considerable practical importance in perfuming confectionery, and lemonades, and for the preparation of fruit essences, and such like.

o-COUMARIC ACID is formed by the decomposition of the diazonium salt of *o*-aminocinnamic acid.

It is odourless and melts at 208° .

THYROXINE.¹ This compound is at one and the same time a phenol and an aminocarboxylic acid, and is of very great biological interest as the active constituent of the hormone of the thyroid gland. It has also been obtained by hydrolysis of synthetically iodinated protein (serum globulin, casein). This active, iodine-containing constituent of the thyroid gland, which regulates metabolism in the animal organism, was first obtained in the pure, crystalline state by Kendall. Its constitution was elucidated, and it was synthesized by C. R. Harington (1926). The formula of thyroxine is:



which shows that the compound may be regarded as a derivative of the protein amino-acid tyrosine (see p. 287) and of iodogorgoic acid (diiodotyrosine, see p. 287), with which it very probably has some genetic connection. The *L*-thyroxine obtained by resolution of the racemate is physiologically three times as active as the *D*-form.

2. Dihydroxycarboxylic acids

PROTOCATECHUIC ACID is contained in the free form in the fruit of *Illicium religiosum*, and is produced from many naturally-occurring substances, e.g. from catechins (p. 566), from different resins, the colouring matter maclurin (p. 519) and several anthocyanins (p. 563) by fusion with alkali.

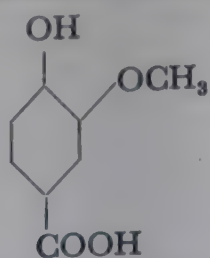
It is prepared synthetically from *p*-hydroxybenzoic acid. This is converted into *m*-chloro-*p*-hydroxybenzoic acid, and the latter is heated with alkali under pressure. The ease with which pyrocatechol is carboxylated to protocatechuic acid is noteworthy. The reaction occurs even on heating with aqueous ammonium carbonate to 140° .

Protocatechuic acid melts at $194\text{--}195^\circ$. It is a strong reducing agent. Its aqueous solution gives a blue-green colour with ferric chloride. This colour changes on addition of a little sodium carbonate or ammonia, becoming first violet and then red.

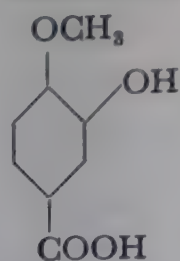
On heating, protocatechuic acid breaks down into pyrocatechol and carbon dioxide.

¹ EDWARD CALVIN KENDALL, *Thyroxin*, New York (Chemical Catalog Co.), (1929).

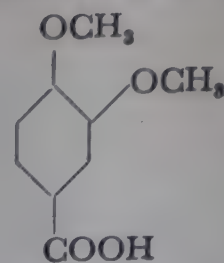
Two isomeric monomethyl ethers, and one dimethyl ether are derived from it:



Vanillic acid,
m.p. 205–206°

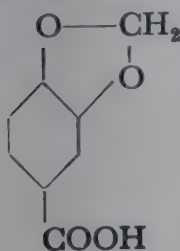


isoVanillic acid,
m.p. 250°

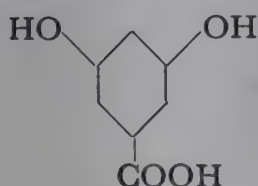


Veratric acid,
m.p. 179°.

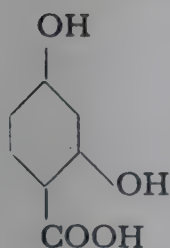
Vanillic acid is produced by the oxidation of vanillin, coniferin, and acetyl-eugenol, and by the alkaline hydrolysis of the colouring matter of the pæony (pæonin). Veratric acid occurs in the free state in the seeds of *Sabadilla veratrum* and has been repeatedly found as a degradation product of alkaloids.



PIPERONYLIC ACID, the methylene ether of protocatechuic acid, melts at 228°.

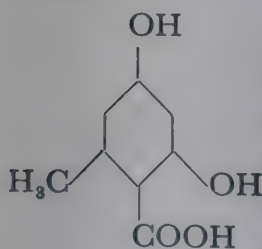


α -RESORCYLIC ACID, m.p. 232°. This acid is used in the synthesis of azo- and oxazine dyes. It is prepared by fusing the potassium salt of 3 : 5-disulphobenzoic acid with caustic alkali. It gives no coloration with ferric chloride.



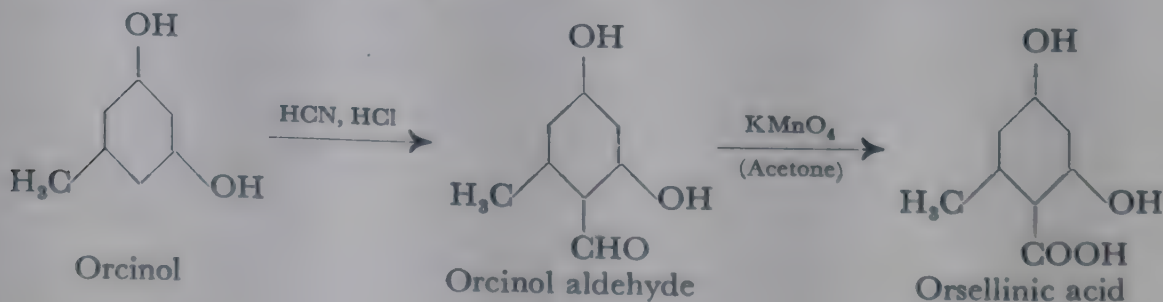
β -RESORCYLIC ACID, m.p. 213°, is formed by heating resorcinol with ammonium carbonate solution. It gives a red colour with ferric chloride.

γ -RESORCYLIC ACID (2 : 6-dihydroxybenzoic acid), gives a violet coloration with ferric chloride.



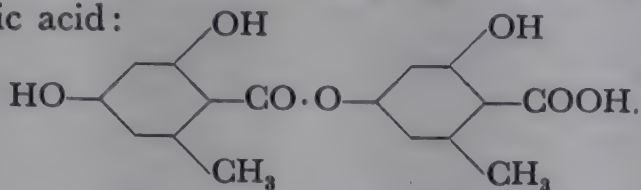
ORSELLINIC ACID. This important hydroxycarboxylic acid is a higher homologue of β -resorcylic acid. It takes part in the structure of many "lichen substances". By this is meant substances with a phenolic character of which the occurrence is generally limited to lichens. Often they are esters of aromatic hydroxy-acids and they have been named by E. Fischer "*depsides*".

The constitution of orsellinic acid is given on the one hand by its degradation to orcinol, which takes place with elimination of carbon dioxide on heating, and on the other hand by its synthesis which is carried out by the oxidation of orcinol aldehyde (obtained by the Gattermann reaction from orcinol, hydrocyanic acid, and hydrogen chloride) with permanganate in acetone solution:



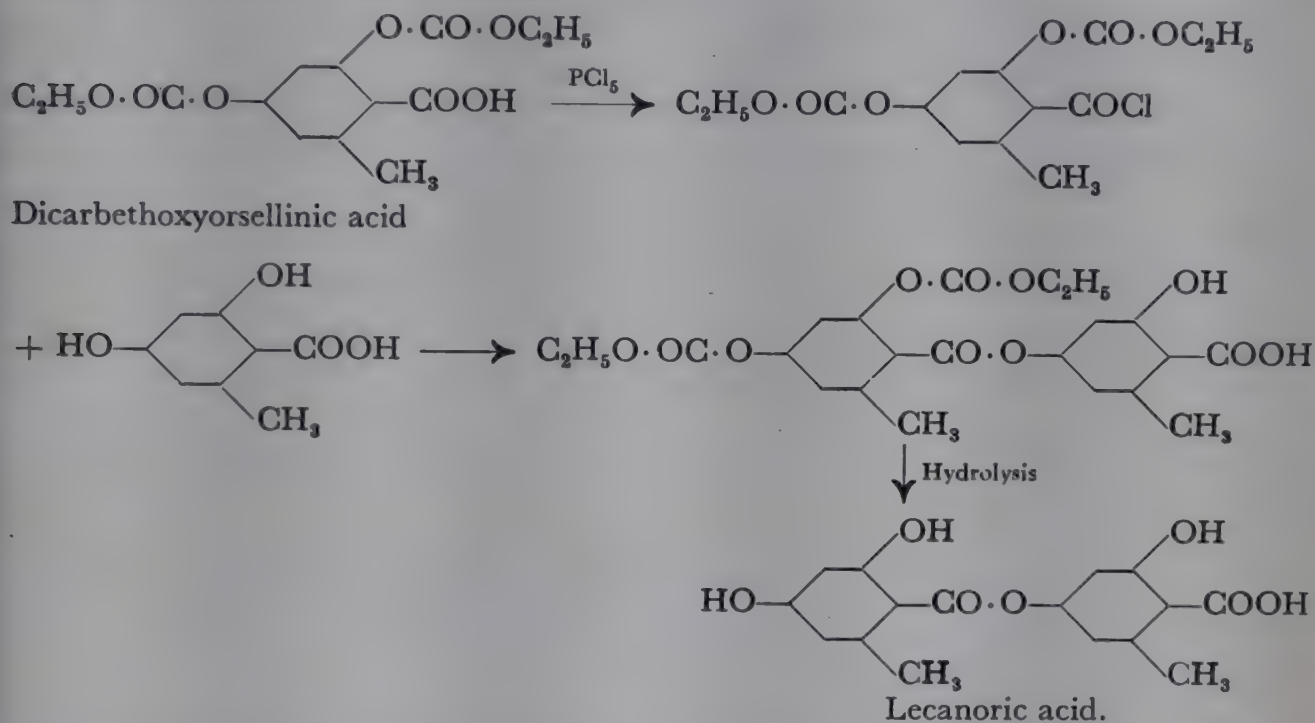
Orsellinic acid melts at 176° with decomposition. Its solution gives a red-violet colour with ferric chloride. It is formed by the hydrolysis of several lichen substances, e.g. lecanoric acid, gyrophoric acid, and evernic acid.

Some lichens, particularly the *Lecanora*, *Roccella*, and *Variola* species, contain a substance called *erythrin*, which is an ester of the tetrahydric alcohol erythritol and *lecanoric acid*. Lecanoric acid itself is a depside and is the ester from two molecules of orsellinic acid:

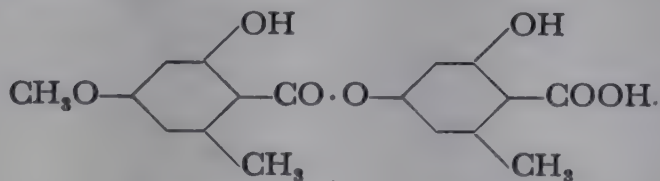


Lecanoric acid, m.p. 166°

Its constitution has been settled beyond doubt by synthesis (E. Fischer). The starting material for this is carbethoxylated orsellinic acid. The following scheme shows the course of the synthesis:



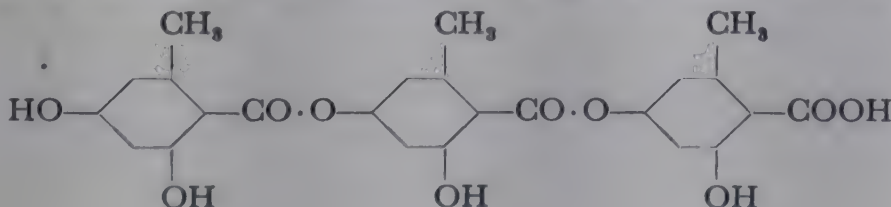
Evernic acid is a monomethyl ether of lecanoric acid. It too is a lichen acid (occurring in various kinds of *Evernia*):



Evernic acid, m.p. $168-169^{\circ}$

It breaks down on careful hydrolysis into one molecule of orsellinic acid and one molecule of evernicinic acid (orsellinic acid 4-methyl ether).

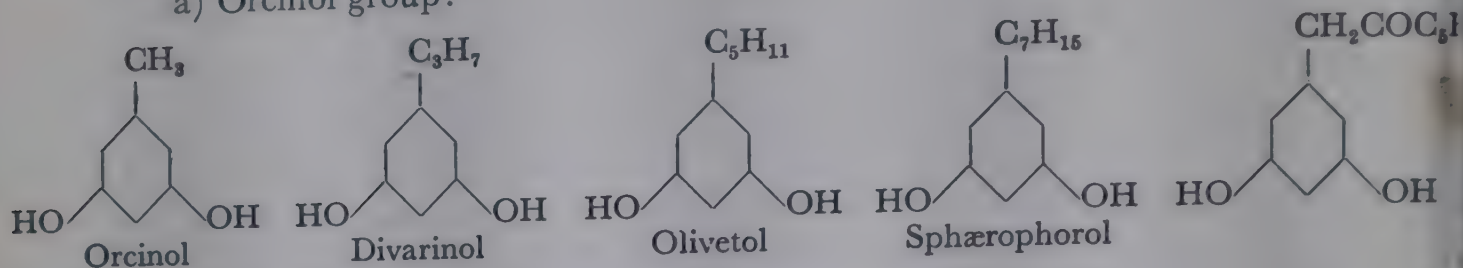
Gyrophoric acid, a compound from *Gyrophora esculenta* is, according to the investigations of Asahina, a tridepside, built up of three molecules of orsellinic acid:



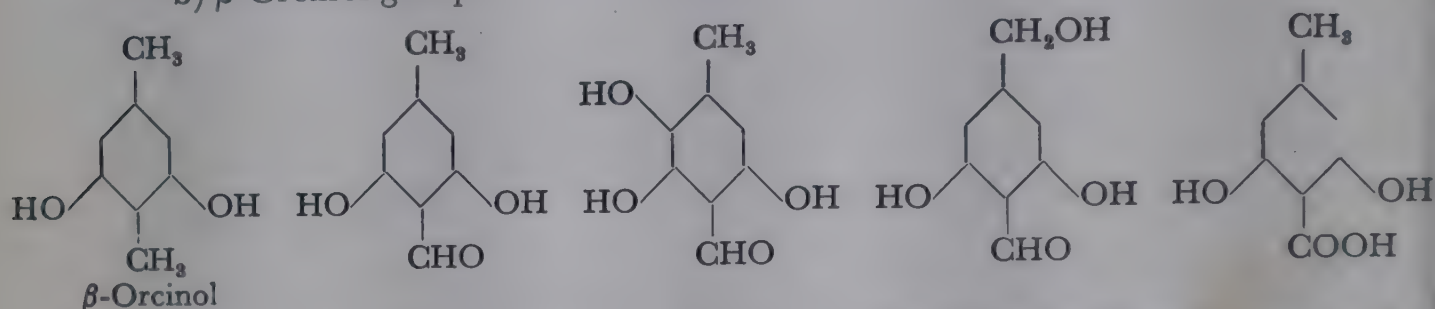
It melts at about 220°. Gyrophoric acid has been synthesized.

The constitutional formulæ of many other naturally-occurring depsides have been elucidated more recently, especially by the work of Asahina. The hydroxy-carboxylic acids, which take part in the structure of these substances, are derived for the most part from the following phenols:

a) Orcinol group:



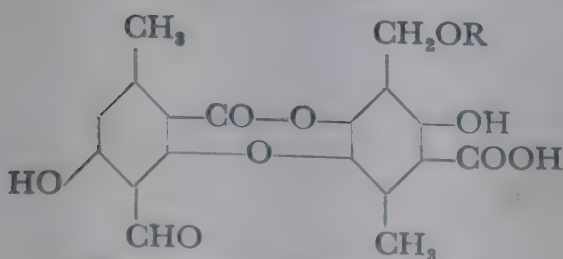
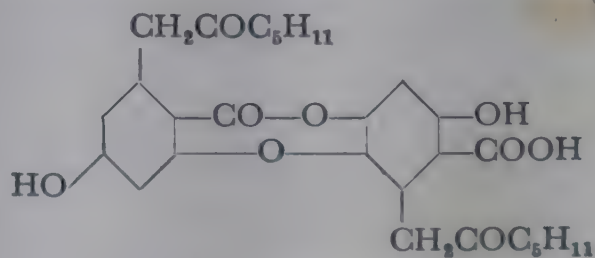
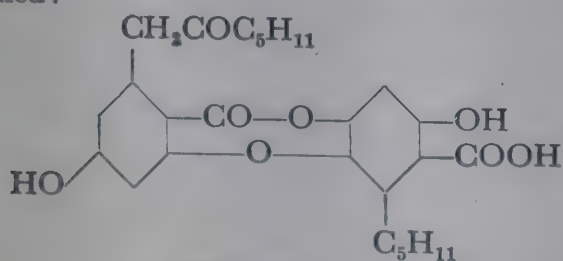
b) β -Orcinol group:



In addition to these depsides, which are readily hydrolysed by alkalis and enzymes, some lichens contain substances which are also made up from polyhydroxybenzenecarboxylic acids, but which, in contrast to the depsides, cannot be broken down into their individual components by means of alkali. Asahina calls these *depsidones*. In them the two aromatic nuclei are linked together by an oxygen atom, as in ethers.

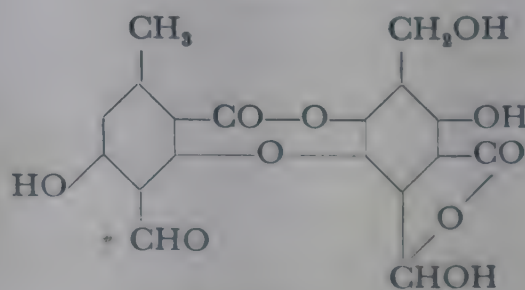
The phenolcarboxylic acids, which have been recognized as the parent substances of the depsidones, are derived from the same phenols as the depside-phenolcarboxylic acids, i.e. from the above-mentioned phenols of the orcinol and β -orcinol groups.

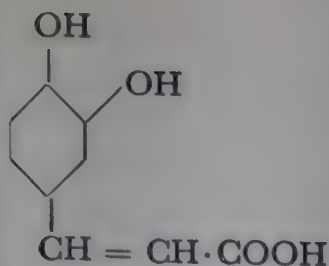
As examples, the following four constitutional formulæ of depsidones may be mentioned:



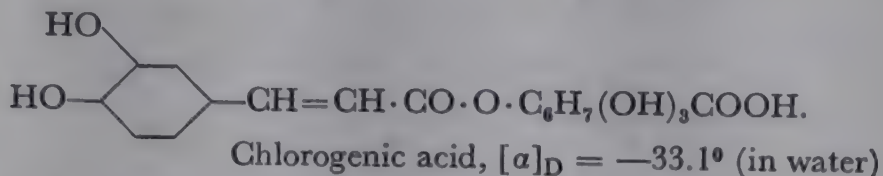
Cetraric acid: R = C₂H₅

Fumaro-protocetraric acid: R = COCH=CHCOOH





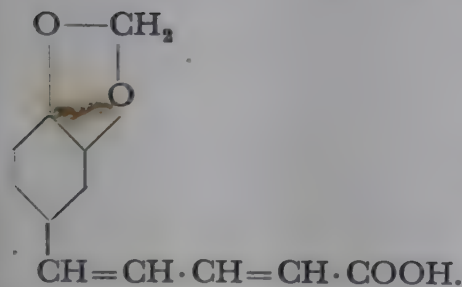
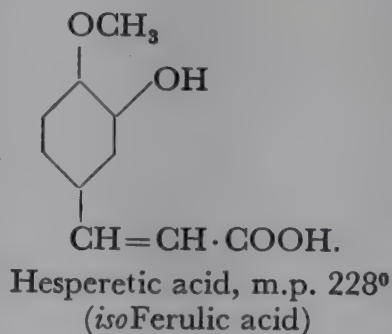
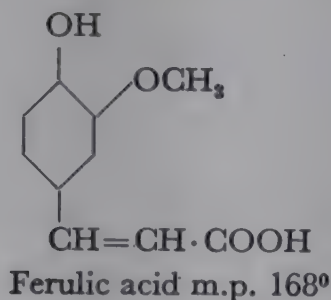
CAFFEIC ACID is very widely spread in plants in the form of derivatives. It has been detected, for example, in hemlock and pine resin, and has been extracted with alkali from the bark of *Cinchona cuprea*. The compound is obtained by the degradation of eriodictyol (see p. 559), and particularly of *chlorogenic acid*, which occurs in considerable quantities in the coffee bean, as the potassium salt, combined with one molecule of caffeine. Chlorogenic acid is a depside which is made up of one molecule each of caffeic acid and quinic acid (see p. 689):



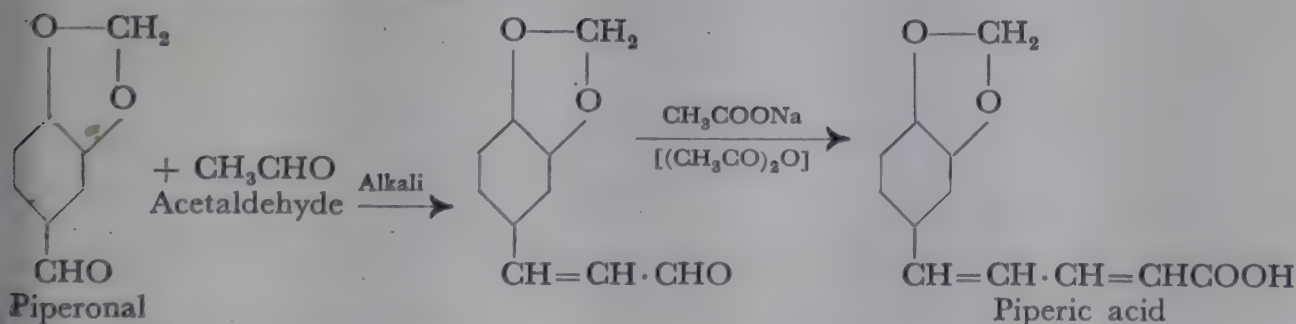
On hydrolysis it breaks down into its components.

Caffeic acid is soluble with difficulty in both cold and hot water. It gives a green coloration with ferric chloride and is a powerful reducing agent. On heating, it loses carbon dioxide, and on fusion with alkali it is converted into protocatechuic acid. It can be obtained synthetically from protocatechuic aldehyde by Perkin's synthesis.

Its two isomeric monomethyl ethers are *ferulic acid* (from ferula resin and black-fir resin, from homoeriodictyol), and *hesperetic acid* (e.g. from hesperetin (see p. 559)):



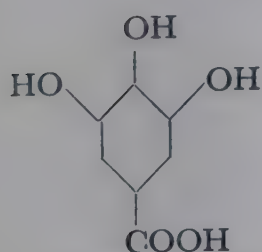
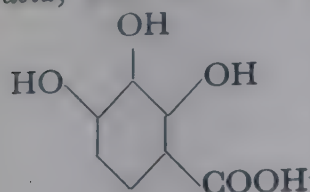
PIPERIC ACID. The piperidide of piperic acid is the sharp tasting chief alkaloid of pepper (piperine, see Ch. 66, 4.). Piperic acid is obtained from this by hydrolysis. It is made synthetically from piperonal:



Piperic acid melts at 215° , and is almost insoluble in water. It is converted into piperonylic acid by means of permanganate, and dissolves in concentrated sulphuric acid with a red colour.

3. Trihydroxycarboxylic acids

Two monocarboxylic acids are derived from pyrogallol, *pyrogallol-carboxylic acid*, and the very much more important *gallic acid*.

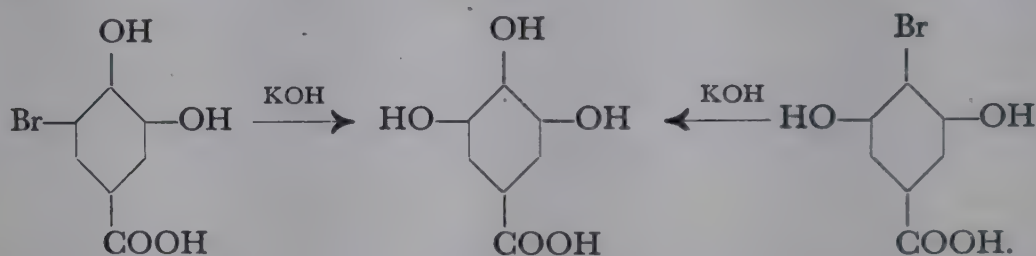


PYROGALLOL CARBOXYLIC ACID is made from pyrogallol by heating with ammonium or potassium bicarbonate solution. The compound crystallizes as a hydrate. If heated for a long time at 195–200°, fusion takes place with elimination of carbon dioxide.

GALLIC ACID is one of the most widely spread of plant acids. Gallnuts, Aleppo galls, divi-divi, sumach, tea leaves, oak bark, pomegranate, etc., always contain some free gallic acid. It occurs in particularly large amounts as esters or glycosides in tannins of the gallotannin type (see p. 545).

Gallic acid is obtained technically from tannin-rich aqueous extracts of gallnuts by hydrolysis with dilute acids or moulds (*Penicillium glaucum*, *Aspergillus niger*). The moulds contain an enzyme, tannase, which breaks down the tannin into sugar and gallic acid.

The compound can be obtained synthetically by fusion of two of the isomeric dihydroxybromobenzoic acids with alkali. Its constitution is also made clear by this method of formation:

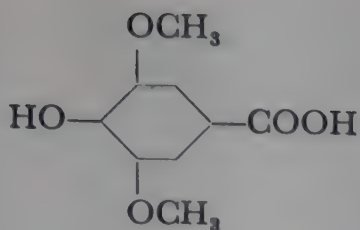


Gallic acid crystallizes in colourless needles, m.p. 222°. It is a powerful reducing agent. It precipitates the metals from solutions of gold and silver salts. It becomes brown on exposure to air owing to oxidation, and this occurs very quickly in alkaline solution.

Ferric chloride gives a blue-black precipitate in aqueous solutions of gallic acid. Use is made of the fact in the preparation of *ink* (nutgall ink). This consists of an aqueous solution of gallic acid (or tannin, see below), which contains ferrous sulphate, gum as a protective colloid, and some sulphuric acid. The sulphuric acid serves to prevent, or greatly to delay, the oxidation of the ferrous salt by atmospheric oxygen, and the consequent deposition of the blue-black precipitate.

When the ink is put on to paper, the sulphuric acid is soon neutralized by the inorganic constituents of the paper (alumina, etc.). The oxidation of the ferrous salt is now no longer prevented, and consequently a blue-black, complex ferric gallate is formed. The writing becomes deep black. In order to impart some colour to the ink at the beginning some indigo and Alizarin blue are added.

Considerable quantities of gallic acid are also used in the dyestuffs industry. The anthraquinone dyes, anthragallol (see p. 597), rufigallic acid (see p. 598), Anthracene brown (see p. 598), the oxazines gallocyanin and gallamine blue (see p. 622), galloflavin, etc., are derivatives of gallic acid. Finally, the compound also finds a limited use in medicine. The bismuth preparation and antiseptic, dermatol, the basic bismuth salt of gallic acid, $C_6H_2(OH)_3.COOBi(OH)_2$, is very well known. It has recently been formulated as a coordination compound of bismuth.



Of the methyl ethers of gallic acid, *syringic acid* (m.p. 203°) commands the greatest interest, since it is obtained by the degradation of many natural substances (e.g. syringin, oenin, malvin, and other anthocyanins (see p. 564) etc.). The glycoside of syringic acid has been isolated from the bark of *Robinia pseudacacia*.

4. Tannins¹

By the term "tannin" was originally understood amorphous compounds, which possessed the property of converting skins into leather, of precipitating solutions of glue, and of giving insoluble precipitates with alkaloids and lead salts. Some tannins, e.g. gallotannin, gelatinize alcoholic solutions of arsenic acid. Many give blue or green colorations with ferric chloride.

As the chemical investigation and purification of the tannins proceeded, the class of tannins has been extended. Not only were several tannins obtained in the crystalline state, but others, such as the simplest galloylhexoses, which are very similar in their constitution to the typical tannins, but which do not give precipitates with glue, alkaloids, arsenic acid, etc., were discovered.

From the chemical point of view it is convenient to divide the tannins into two groups (Freudenberg):

(a) those which are esters, and which are broken down by hydrolysis. They are usually (but not always) derived from gallic acid, and the substances in this class which have been best investigated are Chinese tannin, Turkish tannin, and hamameli-tannin.

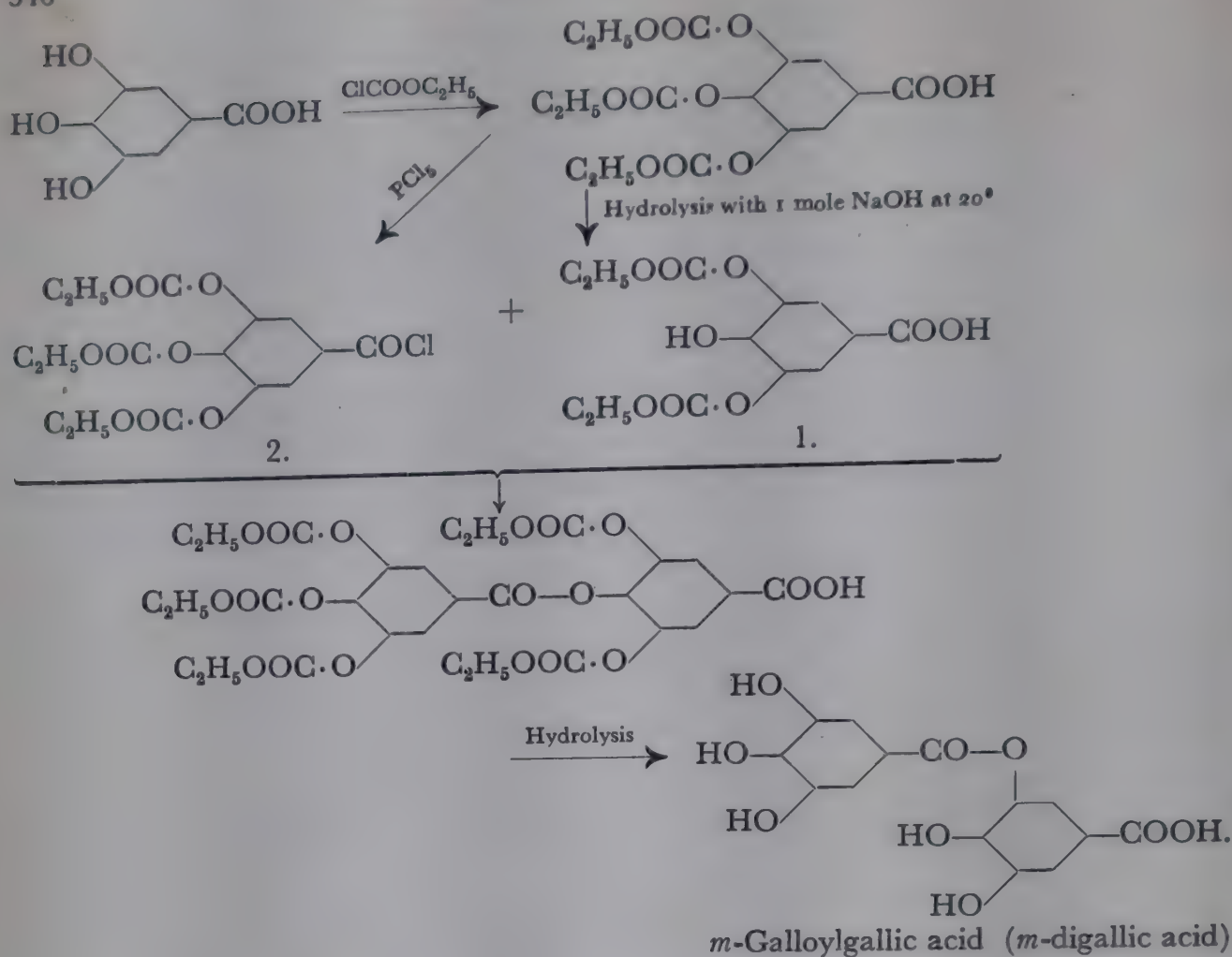
(b) condensed tannins, which are not esters, but of which the nuclei are held together by carbon linkages. The catechins, and other, less well-known, substances belong to this class. They will be dealt with later (p. 566), since constitutionally they resemble the anthocyanins (see p. 562) and flavone derivatives (see p. 556).

The *depsides* stand in close relationship to the tannins of the first class, the hydrolysable tannins and their derivatives. They are, as mentioned above (p. 540), esters of aromatic hydroxy-acids with hydroxy-acids. If two such molecules are linked to each other, a didepside is formed; if three, a tridepside, etc.

Examples of naturally occurring didepsides have already been met with in lecanoric acid, evernic acid, and chlorogenic acid. The synthesis of lecanoric acid is an example of the methods by which similar substances are built up.

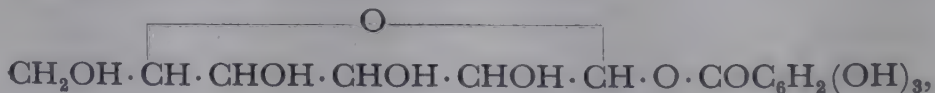
Another important didepside is *m-galloylgallic acid* (or *m-digallic acid*) (E. Fischer). It may be prepared by converting tricarbethoxygallic acid on the one hand by partial hydrolysis into dicarbethoxygallic acid (1), and on the other hand into the acid chloride (2), and condensing the two compounds together to give pentacarbethoxy-*p*-galloylgallic acid. On splitting off the carbethoxy groups from this didepside, *m*-galloylgallic acid is formed, by migration of a gallic acid residue:

¹ See W. FAHRION, *Neuere Gerbemethoden und Gerbetheorien*, Brunswick, (1915). — E. FISCHER, *Untersuchungen über Depside und Gerbstoffe*, Berlin, (1919). — K. FREUDENBERG, *Chemie der natürlichen Gerbstoffe*, Berlin, 2nd ed., (1932). — G. D. MACLAUGHLIN and E. R. THEIS, *Chemistry of Leather Manufacture*, New York, (1945).



meta-Digallic acid is a crystalline substance, melting at 285° . It precipitates glue and thus has tanning properties. It has a taste which is at first bitter, and then sweetish.

By the esterification of glucose with gallic acid and *m*-digallic acid, compounds are produced which, as was shown by E. Fischer, resemble constitutionally the hydrolysable tannins, or are identical with them. Amongst the simplest galloyl derivatives l-galloylglucose is the most interesting.



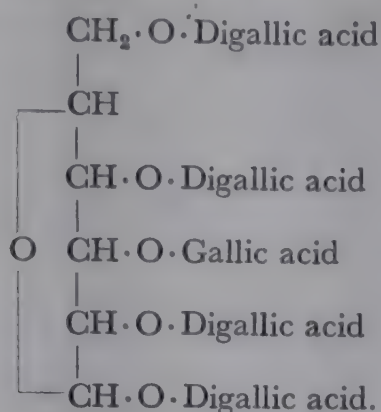
since proved to be identical with the "*glucogallin*" discovered by Gilson in Chinese rhubarb (E. Fischer).

CHINESE TANNIN, the tannin of Chinese galls, is a mixture of poly-galloylated glucose molecules. By repeated fractional precipitation with aluminium hydroxide, it can be separated into fractions, of which the specific rotations in water vary from $+30^\circ$ to $+158^\circ$. In Chinese tannin the five hydroxyl groups of glucose are esterified by gallic acid, *m*-digallic acid, and possibly also trigallic acid residues. On the average, each sugar molecule has nine gallic acid residues. The varying nature of the tannin is largely due to the presence of glucose molecules galloylated to different extents and in different ways. The structure of such a component is thus of the type depicted on the next page.

By partial hydrolysis of Chinese tannin it has been possible to obtain *m*-digallic acid (Herzig), and by synthesis, by the esterification of glucose with *m*-digallic acid, Fischer was able to prepare substances which were very similar in every way to natural Chinese tannin, showing especially the typical reactions of tannins

(precipitation of glue, gelatinization of alcoholic solutions of arsenic acid, etc.).

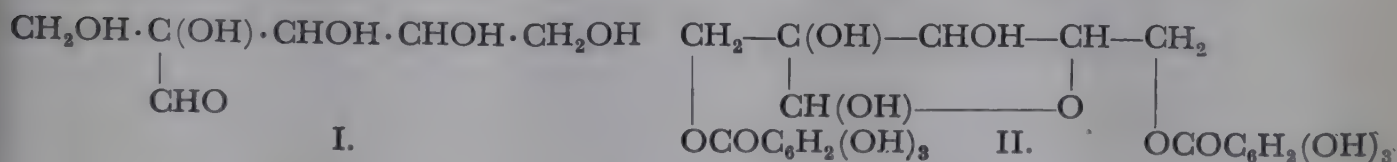
There is, therefore, no doubt that Chinese tannin is a mixture of galloylated glucoses, the extent of esterification being variable.



TURKISH TANNIN. The tannin from Aleppo galls, known as Turkish tannin, is related to Chinese tannin. It too consists of a mixture of galloylated glucoses. The gallic acid content is, however, smaller than in Chinese tannin, and it is far less homogeneous. Besides gallic acid, Turkish tannin contains ellagic acid (see p. 553), which belongs to the tannin molecule, and is apparently linked glucosidically. By fractional precipitation with aluminium hydroxide it is possible to separate it into fractions which differ substantially in their optical rotation, gallic acid content, and ellagic acid content. The differences in glucose content are, however, small. On the average there are probably about 5–6 molecules of gallic acid to one molecule of glucose.

HAMAMELI-TANNIN, a crystalline tannin from the bark of *Hamamelis virginica*, appears to be a digalloylhexose, in which two hydroxyl groups of the sugar are esterified with gallic acid residues (Freudenberg).

The sugar is ascribed the structure I and hamameli-tannin formula II:

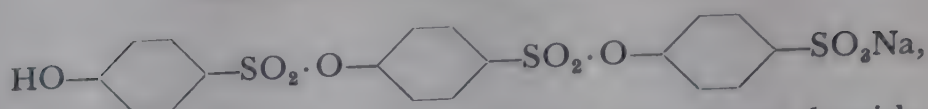


The tannins are used in tanning. They are also used (e.g. gallic acid, p. 544) in the manufacture of ink, as mordants for textiles (see p. 486), and in medicine as astringents in intestinal catarrh. In order to secure that they should only act in the intestines, they are used medicinally mostly in the form of preparations which are insoluble in the stomach, and are decomposed by the alkali in the intestines, e.g. tannalbin (i.e., tannin-protein), tannigen (diacetyltannin), and tannoform (a compound of tannin and formaldehyde).

To the group of hydrolysable tannins belong, moreover, *sumach* (from the leaves of *Rhus cotinus* and *coriaria*), *divi-divi* (from the pods of *Caesalpinia coriaria*), *myrobalans tannins* (from the fruits of *Terminalia chebula*), the *oak, tea, and chestnut tannins*, etc.

Amongst the condensed tannins whose nuclei are connected by carbon-carbon linkages, there are, in addition to the catechins, of which the constitutions are known, and which will be dealt with later (p. 566), the *tannins from the bark and wood of the oak*, the tannin of *horse-chestnut*, *quebracho-tannin* (from South American trees), *quinotannic acid* (from Peruvian bark), etc.

In recent times artificially produced tannins have been put on the market. They can be built up, for example, from phenolsulphonic acids. The compound

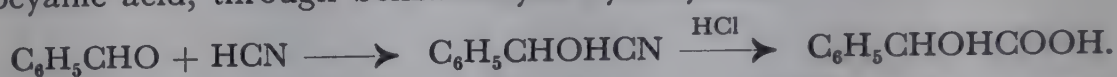


of which the constitution unmistakably recalls that of the depsides, tans skins. The so-called *neradols* (Stiasny), prepared from phenolsulphonic acids and formaldehyde are of particular practical importance. Neradol D consists of condensation products of sulphonated phenols (especially crude cresol) with formaldehyde, and neradol ND is made by condensing naphthalenesulphonic acids with formaldehyde.

B. Aromatic hydroxy-acids with an alcoholic nature

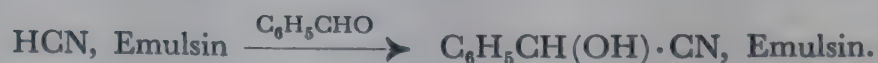
MANDELIC ACID, $\text{C}_6\text{H}_5\text{CHOHCOOH}$. Hydrolysis, with hydrochloric acid, of the glycoside of bitter almonds, *amygdalin* (see p. 184), which is the gentiobioside of benzaldehyde cyanhydrin, $\text{C}_6\text{H}_5\text{CHOHCN}$, gives lævorotatory mandelic acid. The *d*-form is found in another glycoside, *sambunigrin* (from *Sambucus*).

dl-Mandelic acid can be prepared very readily from benzaldehyde and hydrocyanic acid, through benzaldehyde cyanhydrin:



Its resolution into enantiomorphous forms is carried out by means of the cinchonine salt. Another interesting method of resolution was discovered by Marckwald and McKenzie. They esterified *dl*-mandelic acid *incompletely* with the optically active alcohol *l*-menthol, and found that the unesterified residue of the mandelic acid was lævorotatory. *d*-Mandelic acid is therefore more rapidly esterified by *l*-menthol than is *l*-mandelic acid.

Mandelic acid is, moreover, a classical example in stereochemistry. The above mentioned synthesis of mandelic acid from benzaldehyde and hydrocyanic acid leads, of course, to an inactive product. Rosenthaler, however, was able to obtain a partially asymmetric product (see p. 105) by adding some emulsin, i.e. the enzyme of bitter almonds, to the reaction mixture. The mandelic acid thus obtained was lævorotatory, though not optically pure. This phenomenon is probably due to the formation of a molecular compound with the hydrocyanic acid, and afterwards with the benzaldehyde cyanhydrin, which is later broken down:



Since emulsin has an asymmetric structure, an asymmetric system is produced as an intermediate stage during the synthesis, and the further synthetic operations are thus asymmetric.

This "asymmetric" synthesis carried out *in vitro* gives an idea of the ways and means by which optically active substances are built up in the living cell. Doubtless the reaction takes place in a similar way in bitter almonds, where benzaldehyde, hydrocyanic acid, and emulsin occur, and are used for the synthesis of the optically active glycoside of mandelonitrile, *amygdalin*.

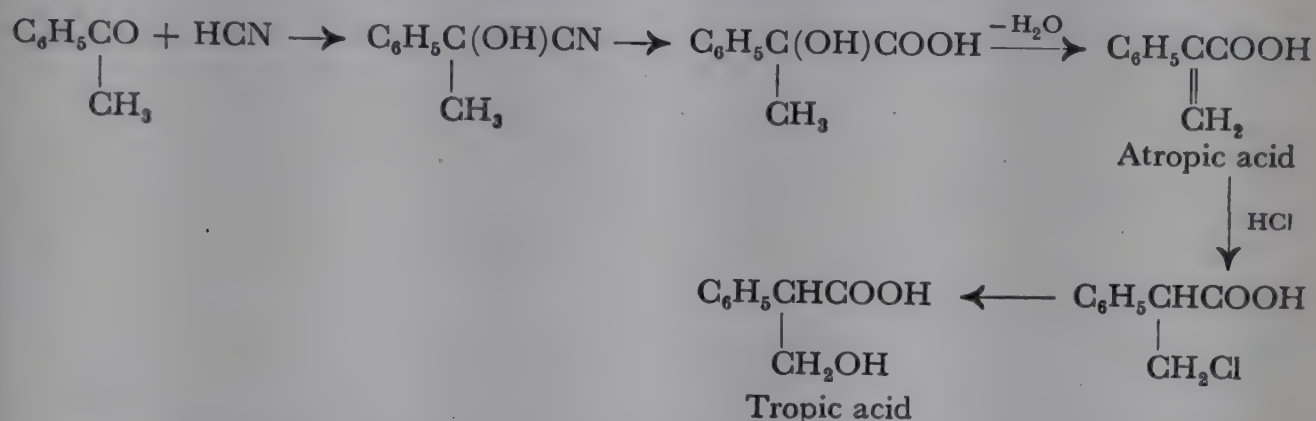
Bredig showed later that the emulsin used by Rosenthaler in the asymmetric synthesis of mandelonitrile could be replaced by the alkaloids quinine and quinidine. The use of quinine gives the glycoside of *l*-mandelonitrile, whilst quinidine gives the *d*-form. It must be assumed in this case, too, that an addition product

of optically active quinine and hydrogen cyanide or benzaldehyde is produced as an intermediate asymmetric product, and is the cause of the asymmetric synthesis. The replacement of emulsin by quinine or quinidine has therefore, considerable theoretical interest, because it shows that relatively simple alkaloids of known constitution can replace the enzyme, of which the chemical nature is not at all clear.

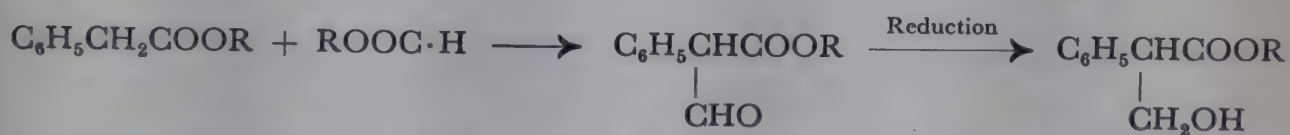
Racemic mandelic acid (also known as *para*-mandelic acid) melts at 119°; the active forms melt at 134° and the specific rotation in water, for the D line, is $\pm 157^\circ$. Mandelic acid is used as a urinary antiseptic.

TROPIC ACID, $\text{C}_6\text{H}_5 \cdot \underset{\text{CH}_2\text{OH}}{\text{CH}} \cdot \text{COOH}$, is contained as an ester in various alkaloids,

e.g. atropine (see Ch. 67), and hyoscyamine (see Ch. 67). The different methods by which it can be prepared have served to confirm its structure. By one method, for example, acetophenone is converted into its cyanhydrin, and then into atropic acid, and finally into tropic acid:



A second synthesis of tropic acid depends on the condensation of phenylacetic ester with formic ester (sodium ethylate being used as condensing agent):



Inactive tropic acid melts at 117°, the optically active acid at 127°. The latter is produced by resolving the racemic form with quinine (Ladenburg and Hundt). Dehydrating agents convert tropic acid into atropic acid (cf. above).

Section III

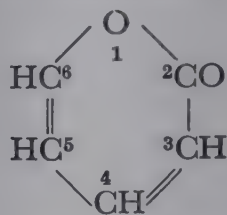
Pyrone compounds. Indigo dyes¹

The pyrone, pyrylium, and indigoid compounds dealt with in this section belong, strictly speaking, to the heterocyclic compounds, and should therefore be treated in Part III of this book. Their close relationship, and genetic connection with purely aromatic substances, particularly the aromatic hydroxy-ketones, hydroxycarboxylic acids, and amino-acids, as well as their considerable chemical, physiological, and, in some cases, technical importance, makes it, however, desirable from the didactic point of view to deal with them here rather than in the last part of this book.

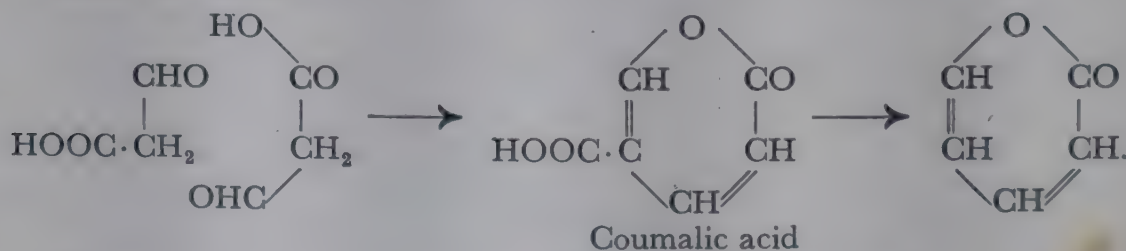
CHAPTER 42. DERIVATIVES OF α - AND γ -PYRONE

A. Derivatives of α -Pyrone

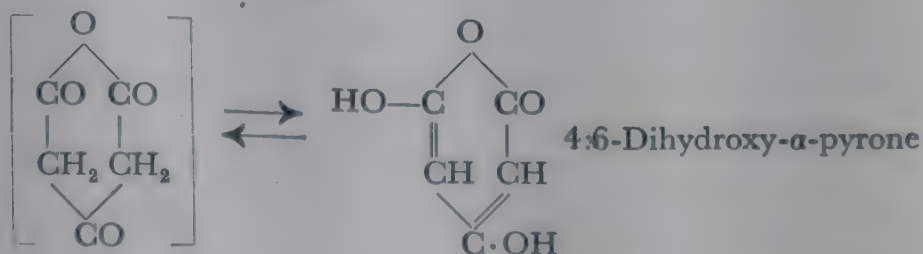
By α -pyrone, or coumalin, is understood the following ring system:



The compound must be regarded as the δ -lactone of a doubly unsaturated acid. Its carboxylic acid — coumalic acid — can be prepared from malic acid by the action of concentrated sulphuric acid (the semi-aldehyde of malonic acid is an intermediate product), and from coumalic acid, by distillation of the mercurous salt, coumalin is obtained:

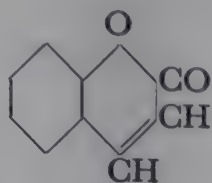
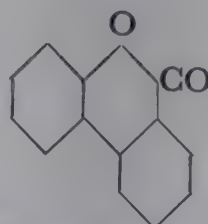


α -Pyrone is an oil smelling like coumarin, b.p. 206–209°, m.p. +5°. It itself has little interest. Acetone-dicarboxylic acid anhydride may be regarded as a dihydroxy-derivative of α -pyrone:



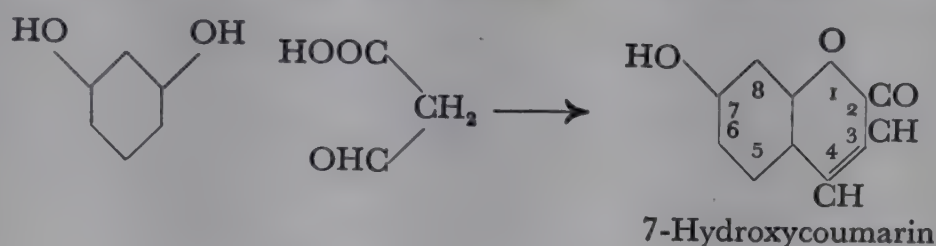
¹ A. G. PERKIN and A. E. EVEREST, *The Natural Organic Colouring Matters*, London, (1918). — F. MAYER, *Chemie der organischen Farbstoffe*, II. Bd., Berlin, (1935).

It reacts readily with diazomethane giving 4 : 6-dimethoxy- α -pyrone. Those compounds obtained by *ortho*-condensation of α -pyrone with one or two benzene nuclei are much more important. They are *benzo- α -pyrone*, or *coumarin*, and *dibenzo- α -pyrone*, or *diphenylmethyloide*:

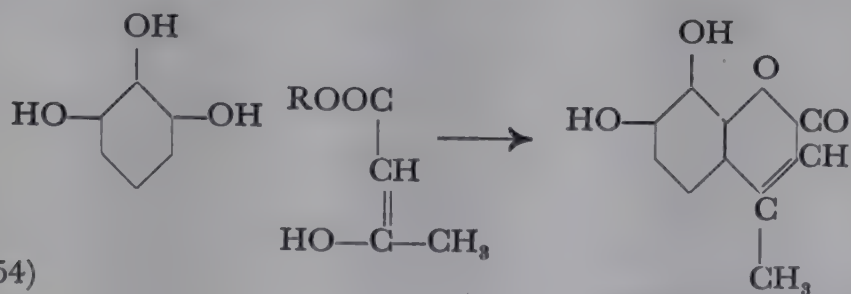
Benzo- α -pyrone, CoumarinDibenzo- α -pyrone (diphenylmethyloide)

Coumarin derivatives.¹ Coumarin itself has already been dealt with on p. 538 as the lactone of coumarinic acid. In addition to Perkin's synthesis of coumarin already described, which can also be used for the preparation of numerous derivatives of coumarin, the following methods are also often used:

(a) Pechmann's synthesis of coumarin. A phenol is heated with malic acid and concentrated sulphuric acid. The malic acid breaks down into malonic semi-aldehyde, which condenses with the phenol to give a coumarin derivative:



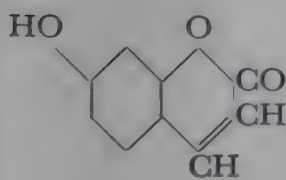
(b) The Pechmann-Duisberg coumarin synthesis. A phenol (usually polyhydric) is treated with acetoacetic ester and a dehydrating agent:



(cf. also p. 554)

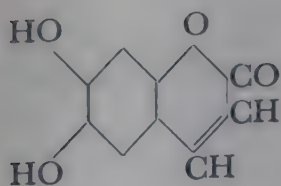
4-Methyl-7:8-dihydroxycoumarin

A great number of hydroxycoumarins are found in plants, of which several can also be obtained by the syntheses outlined above, e.g.:

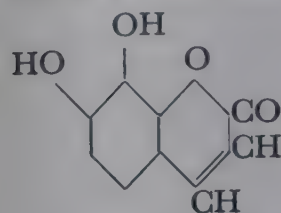


UMBELLIFERONE occurs in the free state in the bark of the spurge-laurel (*Daphne mezereum*) and is obtained by the dry distillation of resins from some *umbelliferae*. It melts at 224°. The methyl ether of umbelliferone is *herniarin* (from *Herniaria hirsuta* (rupturewort)).

¹ See H. SIMONIS, *Die Cumarine*, Stuttgart, (1916).



ÆSCULETIN occurs as the glucoside *æsculin* (glucose radical in the 6-position) in the bark of the horse-chestnut, in wild jasmine (*Gelsemium sempervivens*), and various other plants. It melts at 268°. The blue fluorescence of its aqueous solution is characteristic of this dihydroxycoumarin. It can be obtained synthetically from the aldehyde of hydroxyhydroquinone by Perkin's synthesis. *Scopoletin* is the 6-monomethyl ether of æsculetin. Its glycoside, scopolin, is a constituent of the root of *Scopolia japonica* and several other plants.



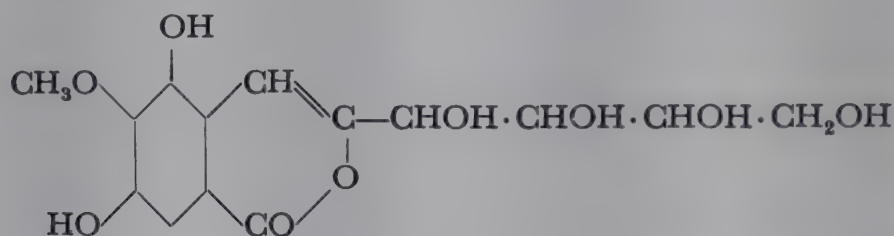
DAPHNETIN. The glucoside daphnin occurs widely in species of *Daphne* (glucose radical in the 7-position). Daphnetin is a weak mordant dye, and fluoresces in solution; m.p. 256°.

LIMETTIN, 5:7-dimethoxycoumarin, occurs in citrus fruits. M.p. 146–147°.

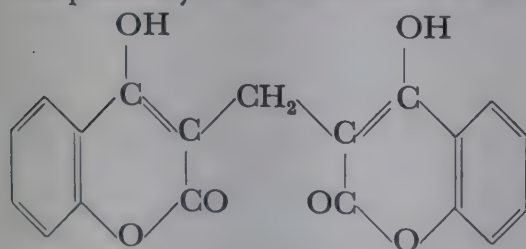
FRAXETIN, 6-methoxy-7:8-dihydroxycoumarin, is the aglucone of the glucoside fraxin, which occurs in the bark of *Fraxinus excelsior* (ash tree). M.p. 227–228°.

For the coumarin derivatives, bergapten, xanthotoxin, etc., see Ch. 59.

A peculiar *isocoumarin derivative* has been discovered by Tschitschibabin. This is *bergenin*, a substance from the root-stems of various members of the *Saxifraga* family. If the formula



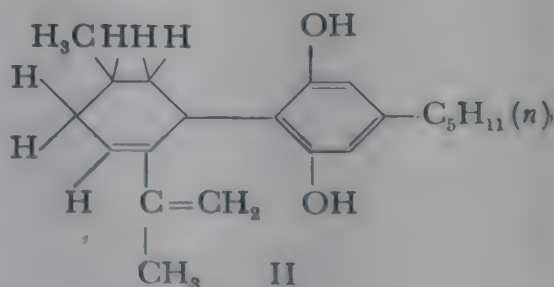
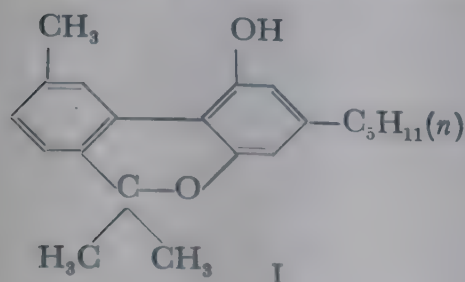
proposed for it is correct, it may be assumed that the compound is produced in the plant by condensation of a molecule of glucose with gallic acid 4-methyl ether.



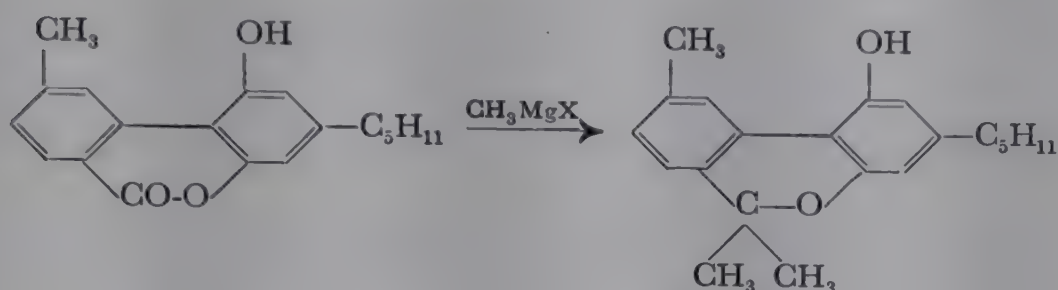
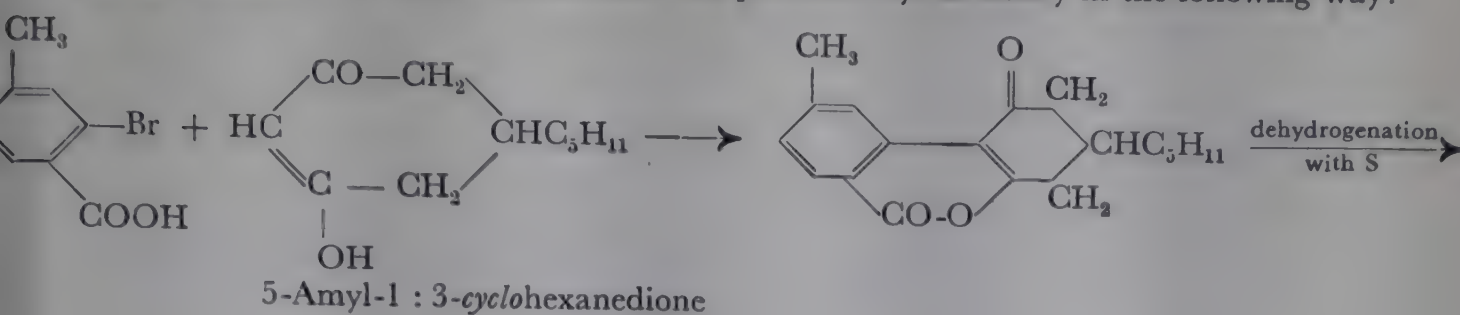
From an American clover hay K. P. Link isolated 3:3'-methylenebis-(4-hydroxycoumarin), which has the property of inhibiting the coagulation of blood in animals feeding on this plant ("sweet clover disease"). The substance can be obtained synthetically from

4-hydroxycoumarin and formaldehyde and is nowadays used in medicine as an anticoagulant ("Dicoumarol").

From the so-called Marihuana extract from the Minnesota wild hemp, Roger Adams isolated *cannabinol* and *cannabidiol*, which are also found in Egyptian hemp oil (Egyptian hashish) (Todd). The former is 1-hydroxy-3-*n*-amyl-6:6:9-trimethyl-dibenzopyran (I); the latter is represented by formula II:

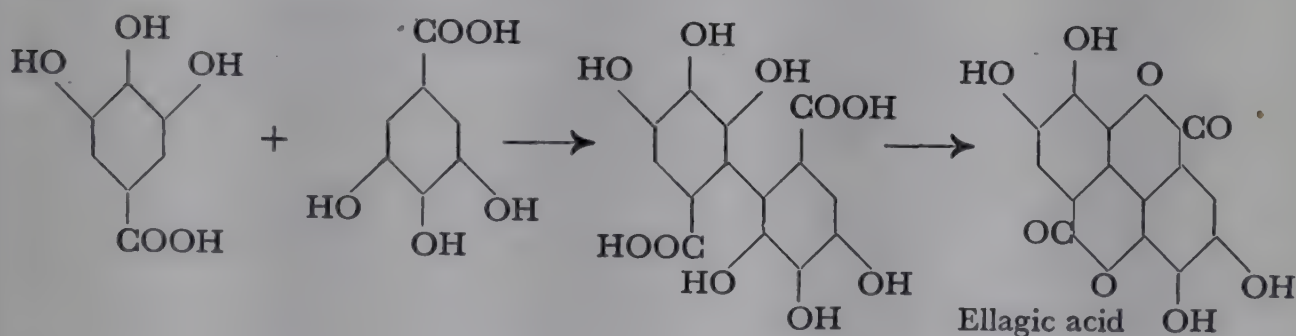


These compounds and also certain synthetic homologues possess the intoxicating properties peculiar to hashish. Cannabinol was produced synthetically in the following way:



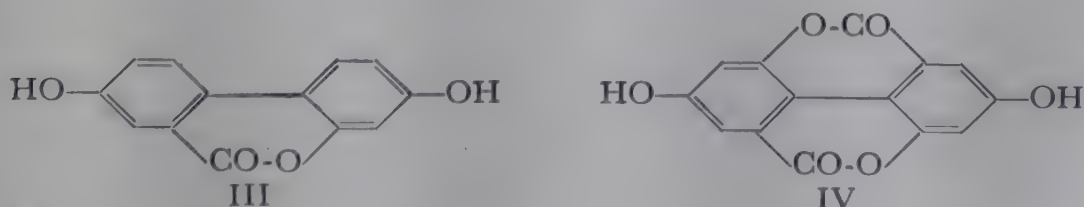
Derivatives of dibenzo- α -pyrone. The most important derivative of dibenzo- α -pyrone is *ellagic acid*. It has already been met with in the previous chapter as a constituent of many tannins. Its pathological occurrence in animal excretions is noteworthy, e.g. in bezoars.

The compound is obtained synthetically by regulated oxidation of gallic acid, e.g. with arsenic acid:



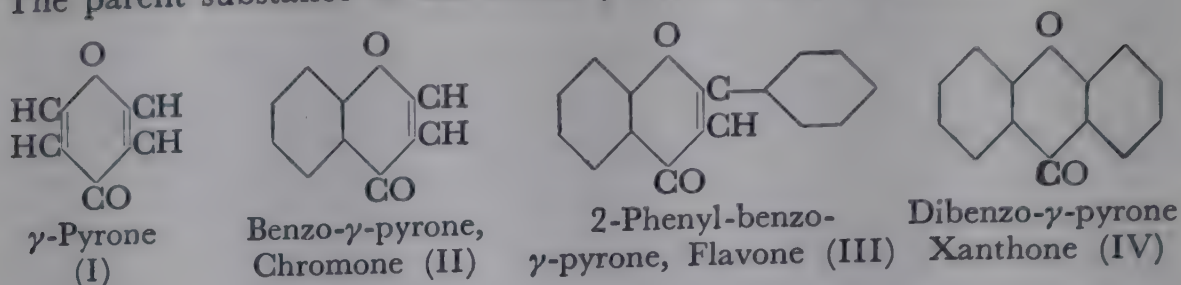
It is a bright yellow crystalline substance, little soluble in water and alcohol, and almost insoluble in ether. On the other hand it is dissolved by alkalis giving solutions with an intense yellow colour. Ellagic acid is a mordant dye, giving a very fast (to light) olive-yellow chromium lake, and therefore finds practical use as a dye. It is also recommended as an intestinal astringent.

E. Lederer has found compounds related to ellagic acid, viz. the yellow pigments III and IV, in castoreum (from scent glands of the beaver (*Castor fiber*)). Both give fluorene when distilled with zinc dust, and 3 : 5-dihydroxybenzoic acid has been obtained by the fusion of IV with alkali:



B. Derivatives of γ -Pyrone

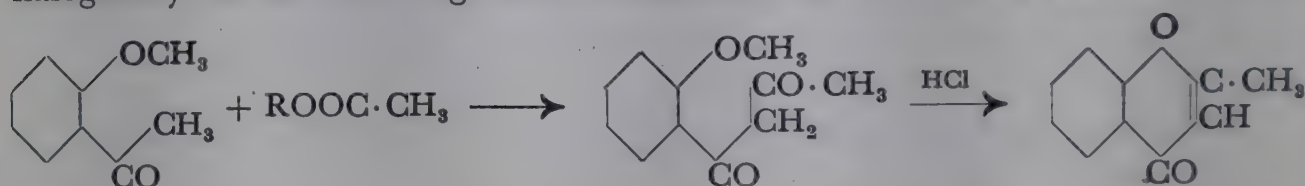
The parent substance of this series, γ -pyrone (I), is known:



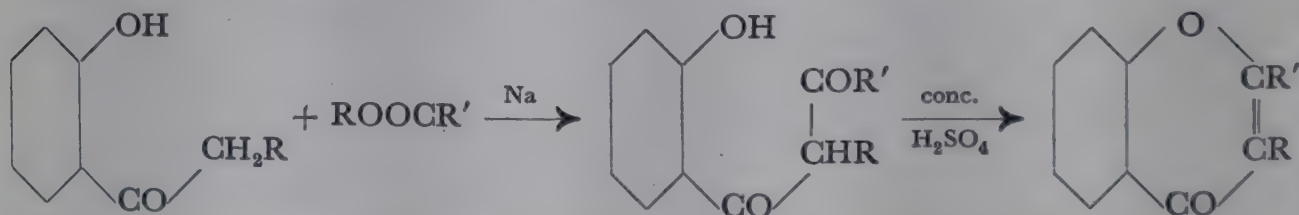
Its simple, non-aromatic derivatives will be dealt with in Ch. 61. Here, benzo- γ -pyrone or chromone (II), flavone (III), *isoflavone* (see p. 560), and dibenzo- γ -pyrone, or xanthone (IV), the parent substances of important yellow plant pigments, will be considered.

Chromone. Of the numerous syntheses known by which chromone and its derivatives can be prepared, the following will be mentioned:

(a) *o*-Hydroxy-acetophenone methyl ethers are condensed with esters of fatty acids by means of sodium to give diketones. These are hydrolysed with concentrated halogen hydracids when ring closure occurs and chromones are formed:

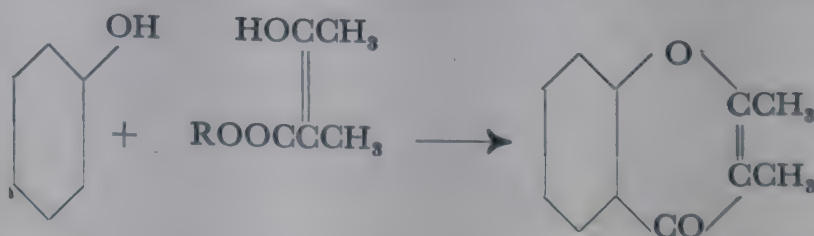


A simpler synthesis makes use of the free acylphenols, in place of the methyl ethers, in the condensation (G. Wittig):



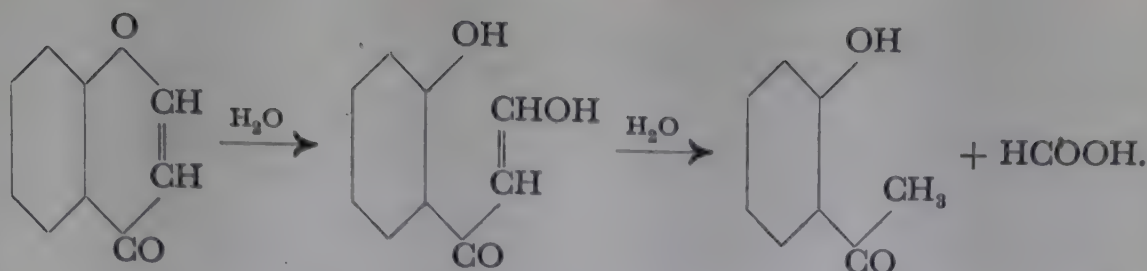
If, instead of the fatty acid ester, oxalic ester is used, a chromone-2-carboxylic acid is obtained, which decomposes on distillation into chromone and carbon dioxide.

(b) β -Keto-carboxylic esters give chromones with some, but not all, phenols, on condensation with phosphorus pentoxide as condensing agent:

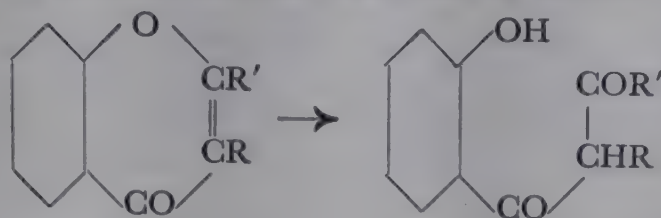


In other cases coumarin derivatives are obtained.

Chromone crystallizes in colourless needles, which melt at 59°. On heating with alkali it breaks down to a hydroxy-ketone. This reaction is typical of chromone compounds, and can be used in the determination of their constitution:

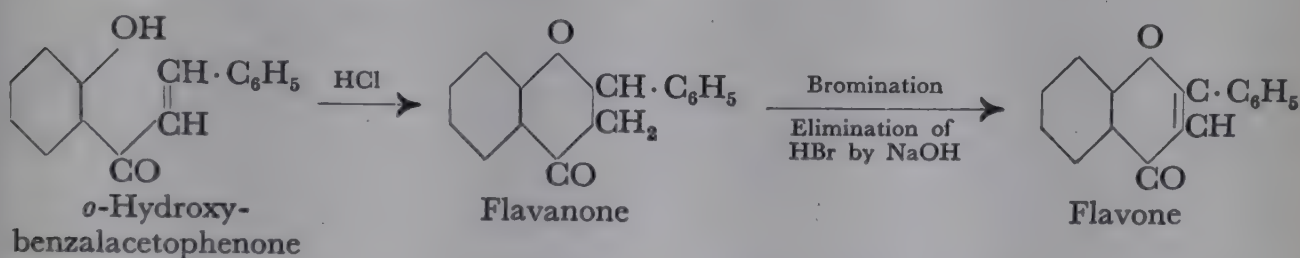


If the hydrolysis is carried out with cold alcoholate solutions, the intermediate product in the hydrolysis, the *o*-hydroxy-diketone, can often be isolated:



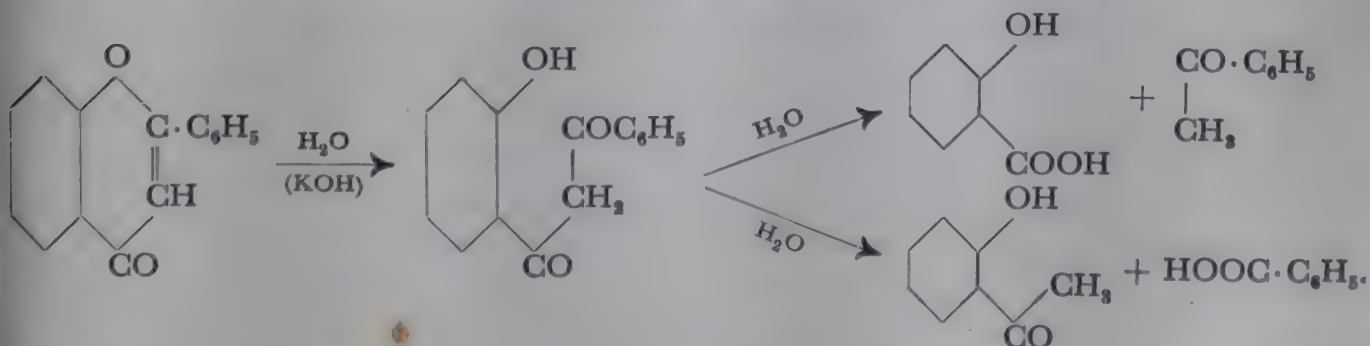
Flavone. Of more importance than chromone itself is its 2-phenyl derivative, flavone, and a series of hydroxyflavones. The investigation of this class of compounds is chiefly due to Kostanecki, who also worked out a large number of useful syntheses, by which these compounds can be obtained relatively easily.

One of these methods is as follows: *ortho*-hydroxy-benzalacetophenone, prepared from *o*-hydroxyacetophenone and benzaldehyde, rearranges into *flavanone* (dihydroflavone) on boiling with dilute alcoholic hydrochloric acid, or better by diluting the alcoholic solution with sodium hydroxide. This is then brominated, and the bromo-derivative treated with alkali, whence it is converted into flavone with elimination of hydrogen bromide:



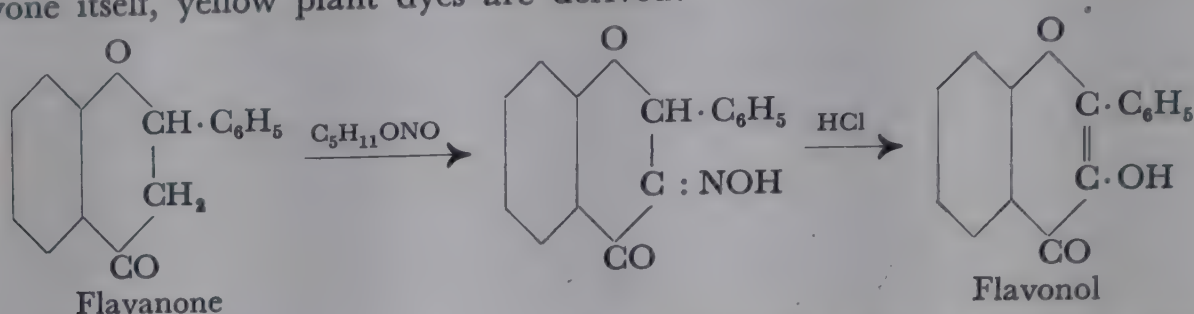
The dehydrogenation of flavanone to flavone can be carried out, according to Löwenbein, in one operation, if the flavanone is treated with phosphorus pentachloride.

Flavone forms colourless needles, which melt at $99-100^\circ$. It is almost insoluble in water. Its solution in concentrated sulphuric acid shows a violet fluorescence. With boiling alkali it is first broken down into *o*-hydroxydibenzoylmethane, which is then further decomposed partly into salicylic acid and acetophenone, and partly into *o*-hydroxyacetophenone and benzoic acid:

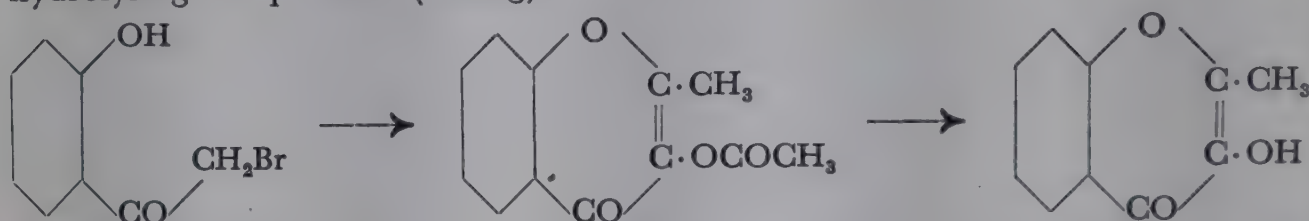


H. Müller has discovered an interesting natural occurrence of flavone. It forms a white, floury coating on the leaves, flower stalks, and seed capsules of different kinds of primula.

By treating flavanone with amyl nitrite in hydrochloric acid, its *isonitroso*-derivative is obtained. This undergoes hydrolysis on boiling with dilute mineral acid. The reaction product is 3-hydroxyflavone, or *flavonol*, from which, as from flavone itself, yellow plant dyes are derived:



Chromonols and flavonols can also be obtained from *o*-hydroxyphenacyl bromides, by heating them with acetic anhydride and sodium acetate, and hydrolysing the product (Wittig):

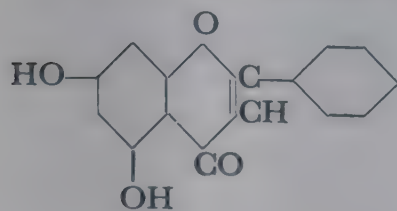


Flavonol crystallizes in yellow needles, which melt at 169° . Its solution in concentrated sulphuric acid shows a violet fluorescence. It is a mordant dye, and dyes cotton mordanted with aluminium hydroxide a bright yellow.

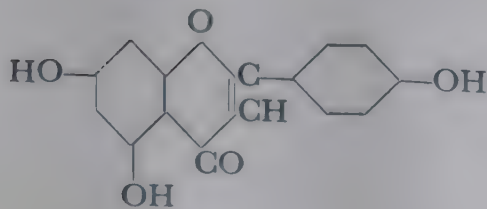
The colours of *yellow* flowers, roots, and woods can be due to various dyes. These can be divided into two large groups. One comprises the so-called *lipochromes* (see Ch. 56). The second class comprises chiefly different *hydroxyflavones* and *hydroxyflavonols*, together with occasional yellow hydroxy-ketones, such as maclurin, etc., which however are genetically connected with the flavones. Finally, a few yellow vegetable dyes belong to the *xanthone group*.

In addition to Kostanecki, A. G. Perkin played a prominent part in the investigation of natural hydroxyflavone and hydroxyflavonol dyes which are very widely spread in plants. The constitution of all these compounds has been verified by degradation, and in most cases also by synthesis.

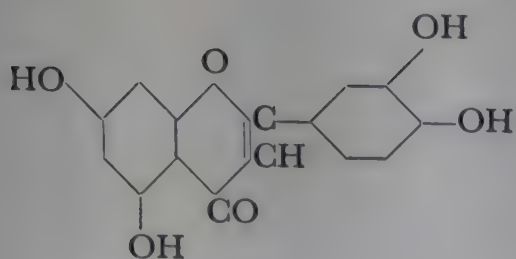
From flavone are derived:



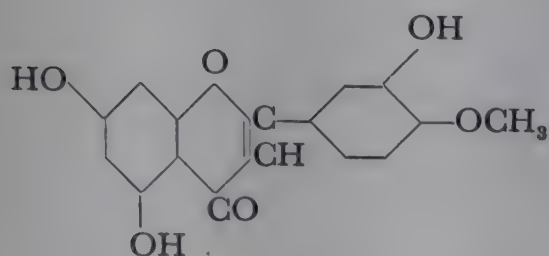
CHRY SIN, occurring in poplar buds. M.p. 275° . It colours wool mordanted with alumina a light yellow.



APIGENIN, occurs partly in the free state, and partly glycosidically in different flowers (*Antirrhinum majus*, *Anthemis nobilis*, *Matricaria chamomilla*). It is also formed by the hydrolysis of the parsley glycoside, apiin. It melts at 347° . Its aluminium lake is pale yellow.



LUTEOLIN, the coloured principle of *Reseda luteola*, which in the dry state is known as the dye "weld" (dyer's weed), was used even in ancient times. Luteolin is also found in the fox-glove. It melts at 328–329°, and colours fabric orange when mordanted with alumina.

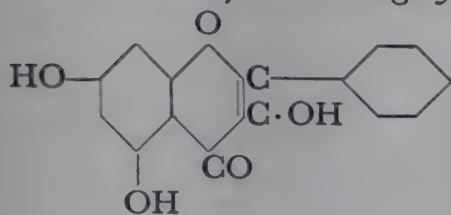


DIOSMETIN, a product of hydrolysis of the glycoside diosmin, was detected by Oesterle in numerous plants.

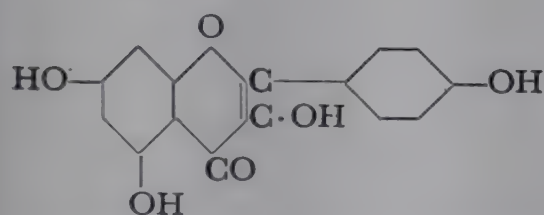
SCUTELLAREIN, 5:6:7:4'-tetrahydroxyflavone, forms, when conjugated with glucuronic acid, scutellarin, which is found in *Scutellaria altissima*. It dyes a brown-yellow colour with an alumina mordant.

TRICIN, 5:7:4'-trihydroxy-3':5'-dimethoxyflavone occurs in a kind of wheat (Khapli wheat) and has also been synthesized (Venkataraman).

Naturally occurring hydroxy-derivatives of flavonol are:

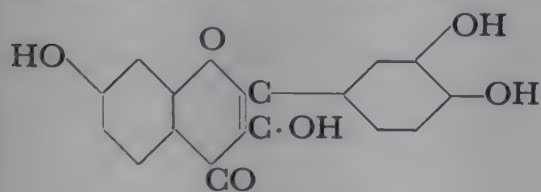


GALANGIN, the flavonol of chrysin, is found in the galanga root, together with a monomethyl ether. Its m.p. is 217–218°. It colours mordanted wool yellow.

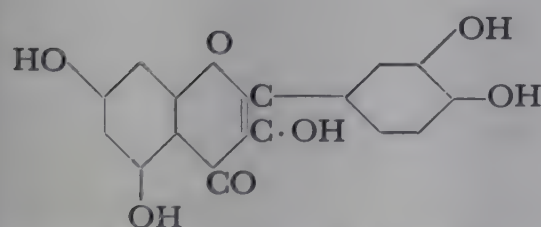


KAEMPFEROL, the flavonol of apigenin. This occurs, partly in the form of glycosides, in many plants (e.g. in senna leaves, in Avignon berries, in the flowers of *Delphinium consolida*, and *Prunus spinosa*, etc.). Kaempferol 4'-monomethyl ether

(kaempferide) is contained in the galanga root. Kaempferol melts at 274°, and gives a yellow aluminium lake.



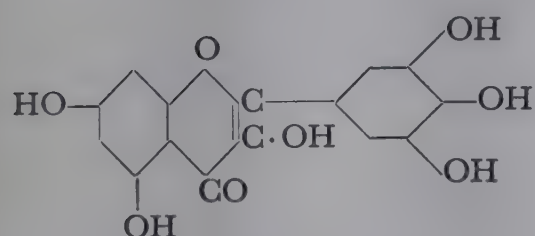
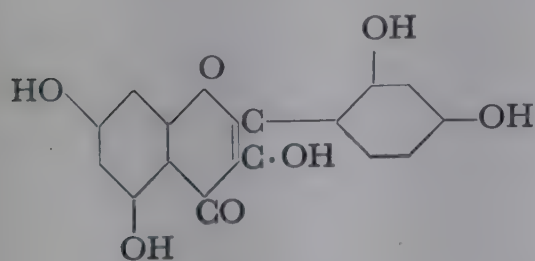
FISETIN, the colouring matter of fustic, is found in fustic wood, combined with glucose and tannin. It melts at 330°. It gives a brown-orange colour with an aluminium mordant.



QUERCETIN, the flavonol of luteolin. This is the most important and most abundant of the dyes of the flavonol group. As the glycoside quercitrin, it occurs in the bark of the American oak, *Quercus tinctoria*, which is still used to-day in the dried and

ground state as a dye for silk and wool. Partly free, and partly in the form of different glycosides, quercetin has been detected in hops, tea, wallflowers, yellow pansies, red roses and in other plants. It melts at 313–314°, and gives an aluminium lake which is brown-orange in colour.

Isomeric monomethyl ethers and a dimethyl ether of quercetin have been discovered in various plants. *Rhamnetin*, quercetin 7-methyl ether is found as a glycoside in berries of the *Rhamnus* family, which have a fairly considerable use in dyeing under the names "buckthorn berries" or "Avignon berries". *Isorhamnetin*, quercetin 3'-methyl ether, occurs in *Cheiranthus cheiri*, *Delphinium zalil*, in senna leaves, and in *Typha augusta*. *Rhamnazetin*, quercetin 7:3'-dimethyl ether occurs together with rhamnetin in "Avignon berries".

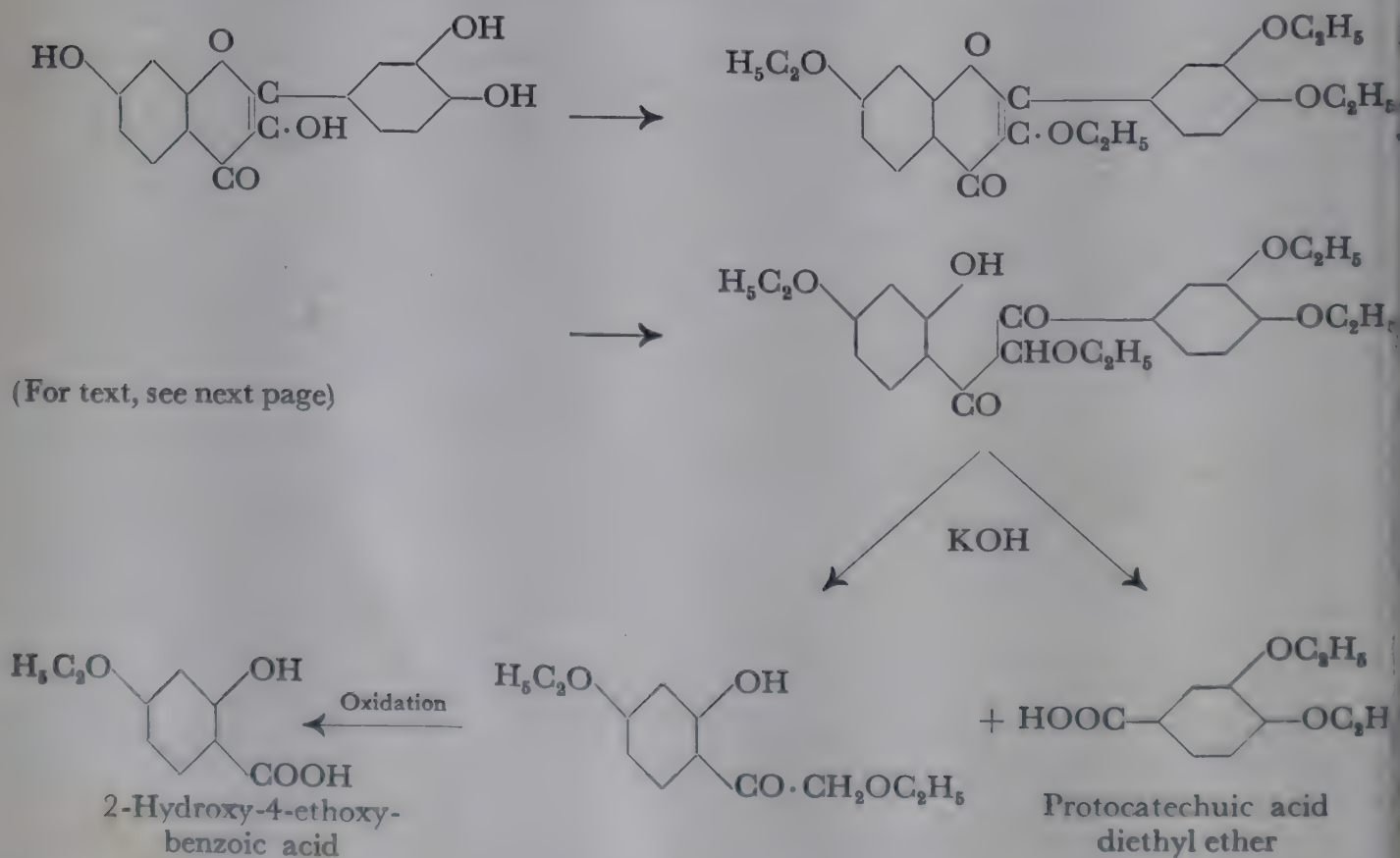


MORIN, is contained, together with maclurin, (see p. 519), in fustic (*Morus tinctoria*) the extract of which is still used to-day in wool-dyeing and cotton printing. It dyes yellow. The melting point of morin is 290°. It is a sensitive reagent for aluminium (green fluorescence in alcoholic solution).

MYRICETIN, occurs as a glycoside in the bark of *Myrica nagi*, and in the leaves various kinds of *Rhus* (*coriaria*, *cotinus*, *metopium*) and in other plants. M.p. 355–360°. The aluminium lake is brown-orange.

Isomeric with myricetin are the pentahydroxyflavonols *quercetagetin*, 3:5:6:7:3':4'-hexahydroxyflavonol (from *Tagetes patula*) and *gossypetin*, 3:5:7:8:3':4'-hexahydroxyflavonol (from yellow mallow). Both have been obtained synthetically by R. Robinson.

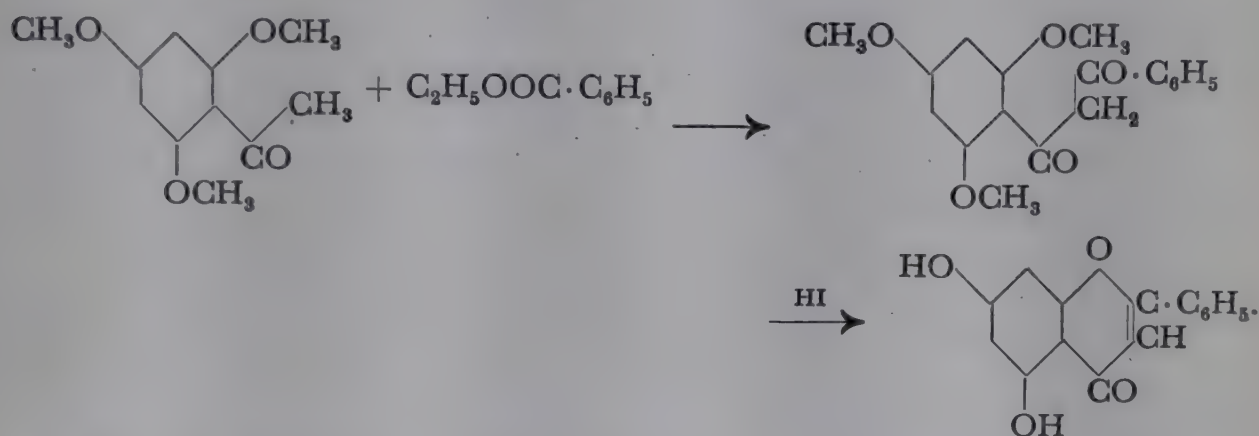
Some polyhydroxy-flavones and -flavonols can be obtained from simpler hydroxy-flavones and -flavonols by oxidation with potassium persulphate. A new hydroxyl group is thus introduced, generally in the *para*-position to one already present (T. S. Seshadri).



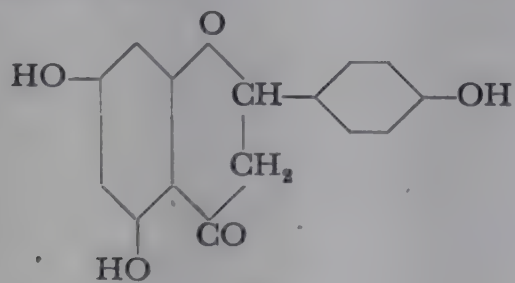
The structure of these hydroxyflavones and flavonols was usually arrived at by alkali fusion or cleavage with aqueous alkalis. Thus, for example, quercetin gives protocathechuic acid and phloroglucinol when fused with alkali, thus making clear the positions of its hydroxyl groups. In other cases it was convenient to alkylate the flavone derivative and then to cleave the product with aqueous alkali. Fisetin was, for example, converted into its tetraethyl ether, and this was degraded to give protocathechuic acid diethyl ether and resorcylic acid monoethyl ether (see previous page).

The constitutional formulæ thus obtained have in many cases been confirmed by the synthesis of hydroxyflavones and hydroxyflavonols. Usually the hydroxyflavone methyl ethers were first prepared and then demethylated. The first synthesis of this kind, that of chrysin, was carried out by Kostanecki in 1899, in the following way.

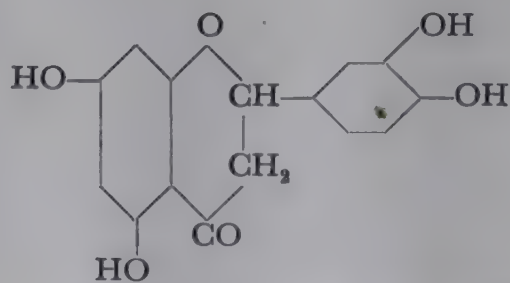
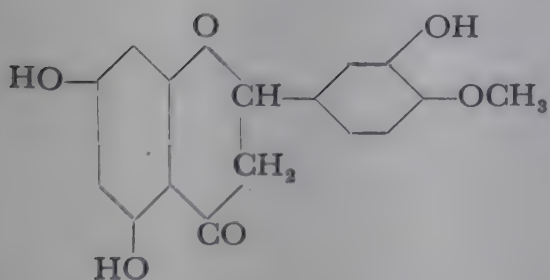
Phloracetophenone trimethyl ether and ethyl benzoate were condensed in the presence of metallic sodium to 2:4:6-trimethoxybenzoylacetophenone. The latter was converted on boiling with hydriodic acid into chrysin, demethylation and ring-closure having taken place:



Flavanone derivatives. In the course of the last few years some natural colouring matters have been recognized as flavanone derivatives, while they were formerly supposed to be derived from chalcone. The most important members of this group are:

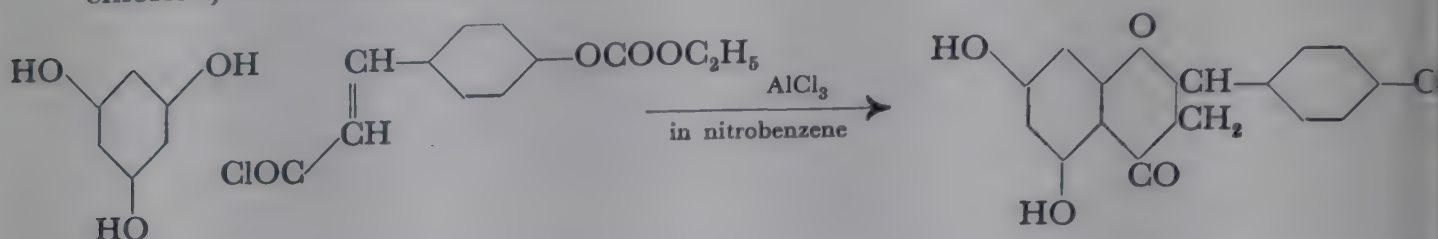


Naringenin

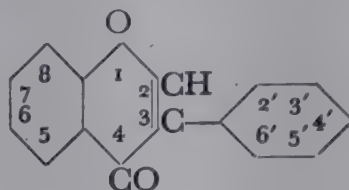
Eriodictyol in *Eriodictyon californicum*

Hesperetin, found as the glycoside "hesperidin" in unripe oranges. It gives on degradation, phloroglucinol and hesperetic acid (see p. 543).

The synthesis of such hydroxyflavanones is carried out, for example, from phloroglucinol, hydroxycinnamic acid derivatives, such as carbethoxy-*p*-coumaryl chloride, and aluminium chloride:



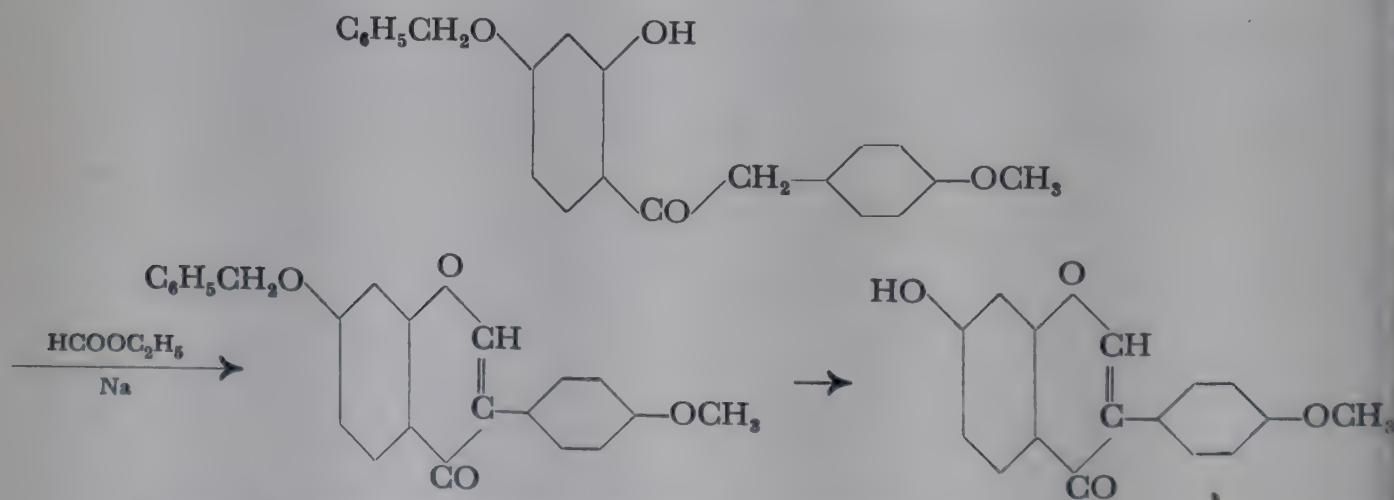
Isoflavone derivatives. Some natural yellow vegetable dyes are derived also from 3-phenyl-benzo- γ -pyrone, or *isoflavone*:



To this class belong *genistein*, or 5:7:4'-trihydroxyisoflavone, from the flowers and leaves of the dyer's broom, *Genista tinctoria* L., and from soya beans (*Soya hispida*) where it occurs as the glycoside *genistin*; *tectorigenin*, or 5:7:4'-trihydroxy-6-methoxyisoflavone (R. Robinson, W. Baker, Y. Asahina); *irigenin* (5:7:3'-trihydroxy-6:4':5'-trimethoxyisoflavone) from the violet root; and *formononetin* (7-hydroxy-4'-methoxyisoflavone).

Walz found in soya beans a further isoflavone glucoside, *daidzin* (7:4'-dihydroxyisoflavone 7-glucoside), which gives *daidzein* on hydrolysis.

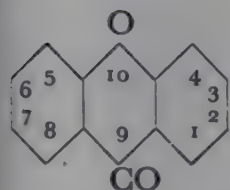
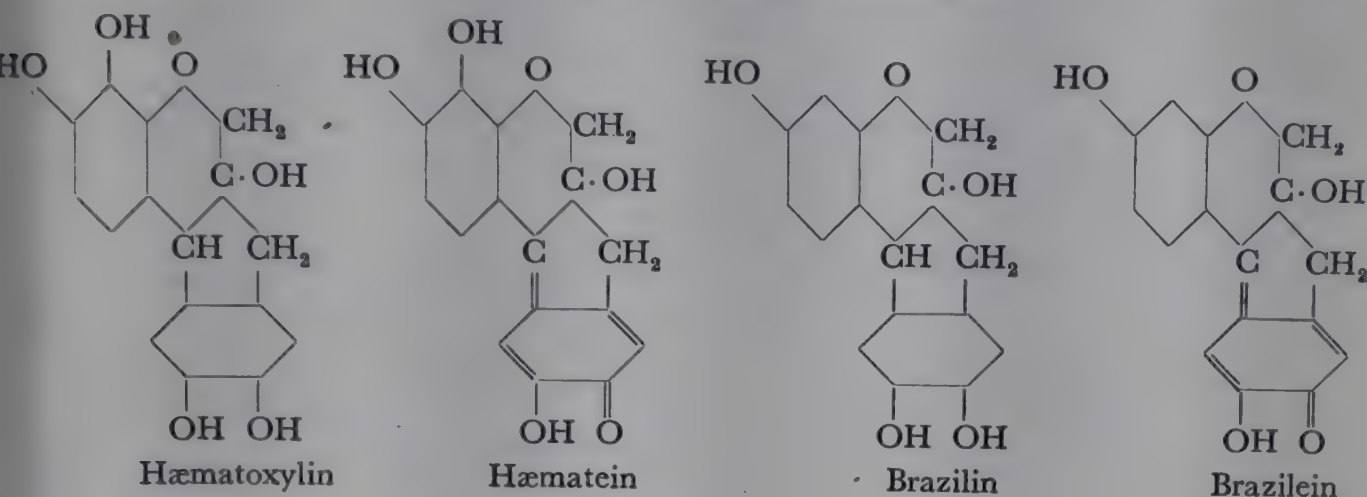
*iso*Flavones can also be obtained synthetically. Thus, for example, formononetin can be obtained by condensation of [2-hydroxy-4-benzyloxyphenyl]-[4'-methoxybenzyl]-ketone, ethyl formate, and sodium:



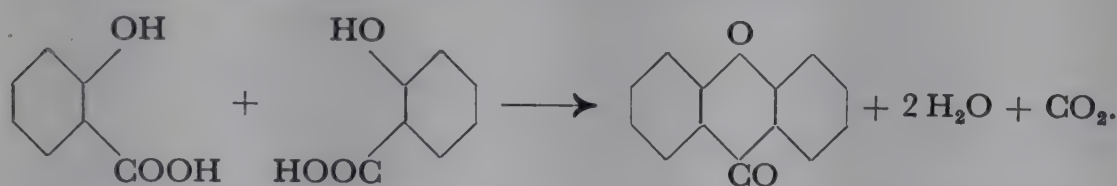
Dyes of brazil wood and logwood. Brazil wood comes from various American species of *Cæsalpinia* (Pernambuco wood, Bahia wood, Lima wood, etc.). In former times, its extracts were largely used in dyeing, and even to-day it is still used in cotton printing, and for dyeing cotton which has been mordanted with sumach or tin salt. *Logwood*, or Campeachy wood, occurs in *Hæmatoxylon campechianum*, and is imported from Central America. Logwood extract belongs even to-day to the most important dyes, and in some work, such as silk dyeing and calico-printing, it is not excelled by any artificial dye. It is a mordant dye,

and is applied to fibres mordanted with metal salts; with alumina it gives a grey-violet colour, with chromium blue-black to black, with iron black, and with tin red-violet.

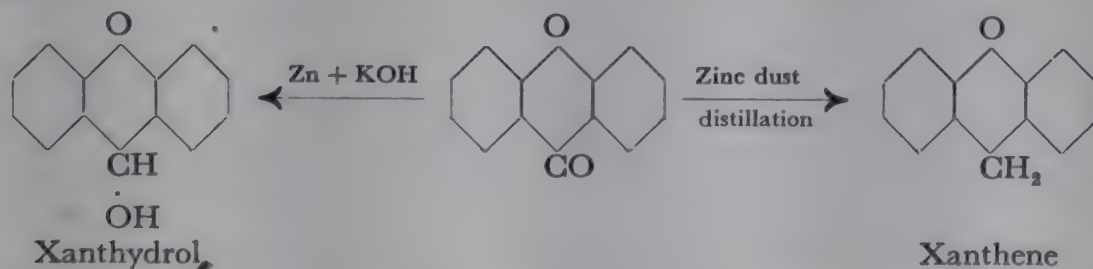
The two dye-woods contain two closely related *colourless* compounds. Brazil wood contains *brazilin*, and logwood *hæmatoxylin*. They are converted on oxidation into two red quinonoid dyes, *brazilein* and *hæmatein*; hæmatein is a hydroxy-derivative of brazilein. Their constitution has been almost completely elucidated. According to Pfeiffer they have the following formulæ, according to which they are to be considered as closely related to the flavone dyes:



Xanthone. Dibenz- γ -pyrone, may be synthesized in various ways, e.g. by heating salicylic acid with phosphorus oxychloride, or better with acetic anhydride:



It forms colourless needles, melting at 173–174°, and is broken down on fusing with alkali to 2 : 2'-dihydroxybenzophenone. With zinc dust and alkali it gives xanthidrol, and by distillation with zinc dust it is reduced to xanthene:

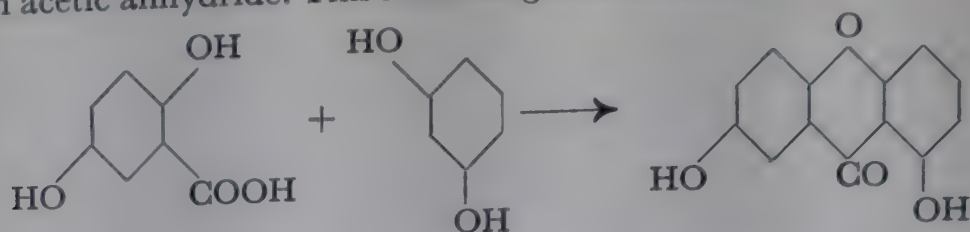


A xanthone perchlorate is known, which is to be regarded as an oxonium salt (see also p. 517 and Ch. 61).

A few hydroxyxanthenes, yellow dyes, are met with amongst naturally occurring substances. Amongst them are:

EUXANTHONE. This is found, conjugated with glucuronic acid in the so-called euxanthic acid, present in "Indian yellow", a painter's colour, which in India is prepared from the urine of cows which have fed on mango leaves (Stenhouse). It

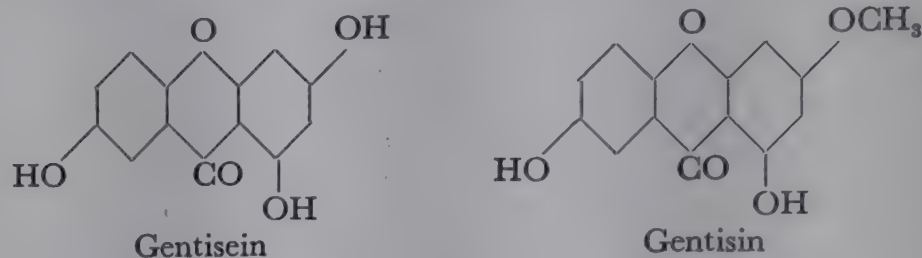
can be synthesized from hydroquinone-carboxylic acid and resorcinol, which are boiled with acetic anhydride. This reaction gives the constitution of the substance:



Euxanthone melts at 240° . It is dark yellow, and its chromium lake has an ochre colour.

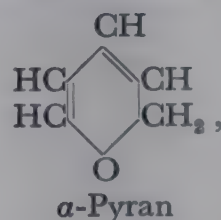
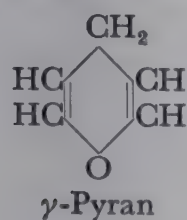
In euxanthic acid, the glucuronic acid radical is attached to the hydroxyl at position 7.

The yellow *gentisin* occurs in gentian root; it is the 3-monomethyl ether of 1:3:7-trihydroxyxanthone, or *gentisein*. The latter has the properties of a mordant dye:

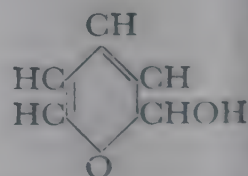
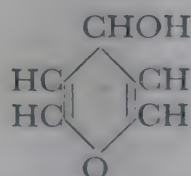
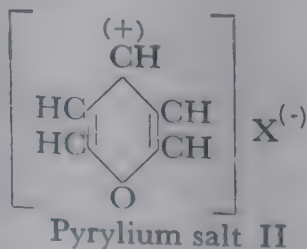
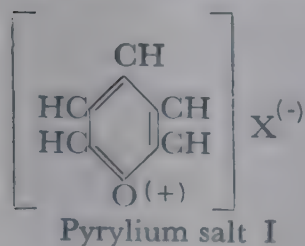


CHAPTER 43. ANTHOCYANINS. CATECHINS

From the two heterocyclic ring systems known as γ - and α -pyran:



which up to the present have neither been prepared in the free state, nor in the form of simple derivatives, are derived not only the α - and γ -pyrones dealt with in the previous chapter, but also salt-like compounds which are called "pyrylium" or "pyroxonium" compounds. In these compounds the basic function is exercised either by the oxygen or a carbon atom. They therefore form a definite group of oxonium or carbonium salts. By the action of alkalis the pyrylium salts are converted into pyrylium bases or carbinol bases, for which the formulæ III and IV come under consideration:

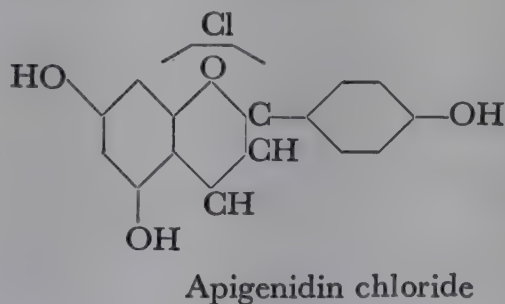
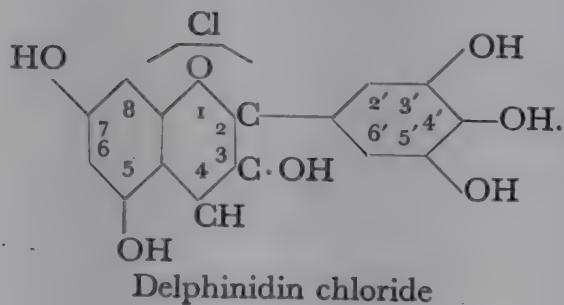
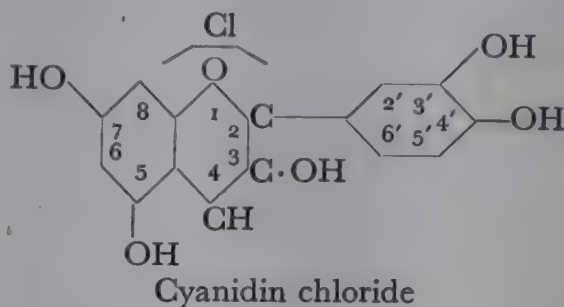
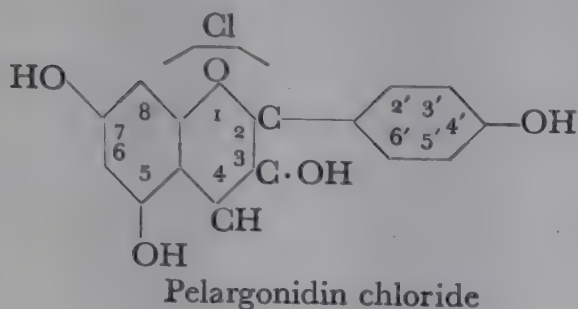


As the investigations of Willstätter have shown, the majority of red and blue flower and berry pigments are derived from the pyrylium radical. They were

called *anthocyanins* even before their constitution had been elucidated. As the following considerations will show they are constitutionally closely related to the yellow flower pigments of the flavone and flavonol series.

All the anthocyanins are ordinarily glycosides. On boiling with acids (also under the influence of certain enzymes) they decompose into a sugar and *anthocyanidins*. The latter are of the nature of pyrylium salts. At present four types are recognized: *pelargonidin*, *cyanidin*, *delphinidin*, and the more rare *apigenidin*, in which the hydroxyl group in the 3-position is absent.

As it is not absolutely certain whether these dyes should be formulated as oxonium or as carbonium salts and whether, in the latter case, the C-atom 2 or 4 is the carrier of the positive charge, their formulæ are given below in the "neutral" formulation that is most usual nowadays.



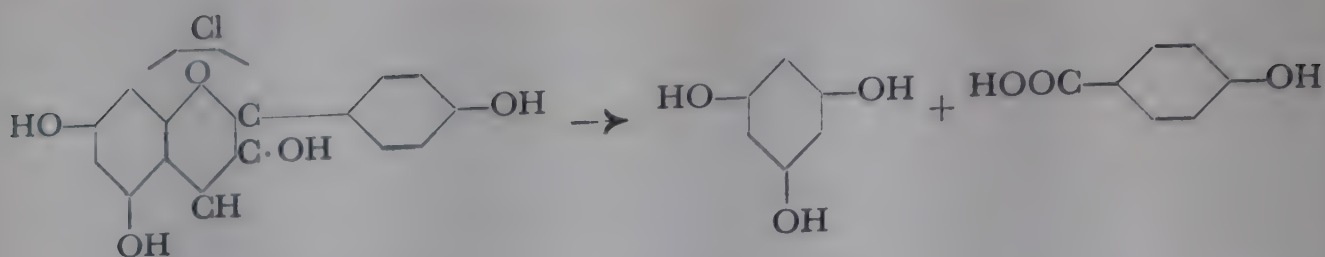
PELARGONIDIN is present as the diglucoside *pelargonin* in the scarlet pelargonium and orange dahlia, and in the form of a monoglucoside, *callistephin*, in asters. The colouring matter of golden balm-mint (*Monarda didyma*) and of species of red-flowering salvia, *monardaein*, is a pelargonidin diglucoside. One molecule of *p*-hydroxycinnamic acid and two molecules of malonic acid also take part in its structure.

CYANIN, a diglycoside of *cyanidin*, is the colouring matter of the red rose, the corn-flower, and the red cactus dahlia. Another cyanidin diglycoside, *mecocyanin*, is the pigment of red poppies. The black cherry contains an anthocyanin, *keracyanin*, in which one molecule of glucose and one molecule of rhamnose are combined with cyanidin. The colouring matter of the plum, *prunicyanin*, is also regarded as a glucorhamnoside of cyanidin. Red whortleberries contain *idæin*, a monogalactoside of cyanidin, while scarlet winter asters, and certain varieties of *Aster chinensis*, blackberries, and elderberries contain a monoglucoside, *chrysanthemin*.

DELPHINIDIN is obtained by hydrolysis of *delphinin*, the pigment of the larkspur, which is furthermore made up of two molecules of glucose, and two of *p*-hydroxybenzoic acid. *Violanin* from violet pansies is also a delphinidin derivative (the sugar components being glucose and rhamnose). The pigment of the wine-red vetch also belongs to this class.

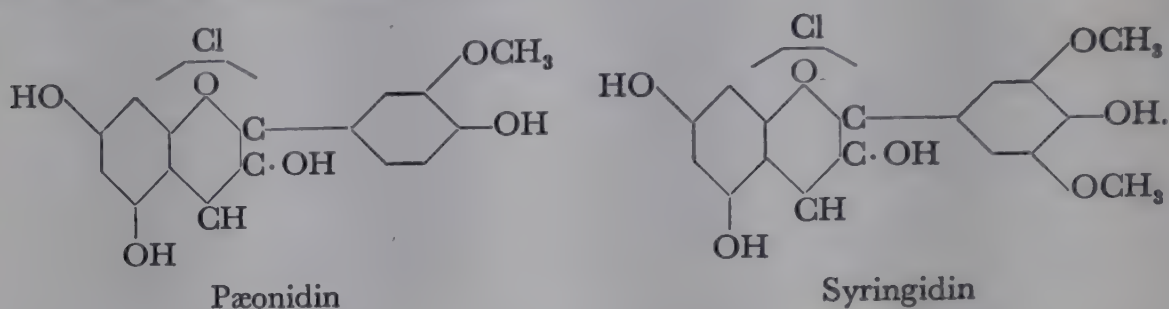
GESNERIN, an apigenidin monoglucoside, occurs in the flowers of *Gesnera fulgens*.

The determination of the constitution of the four anthocyanidins has been carried out by fusion with alkali. Pelargonidin is thus broken down into phloroglucinol and *p*-hydroxybenzoic acid:



Cyanidin furnishes protocatechuic acid under the same conditions, in addition to phloroglucinol, while delphinidin gives gallic acid.

Many other flowers and berries contain methyl ethers of these three fundamental substances. The pigment of the pæony, *pæonin*, is a diglucoside of *pæonidin*; the pigment of the blue mallow, *malvin*, contains a dimethyl ether of delphinidin, *syringidin* (it contains in addition two molecules of glucose), from which is also derived the colouring matter of wine, *œnin*:

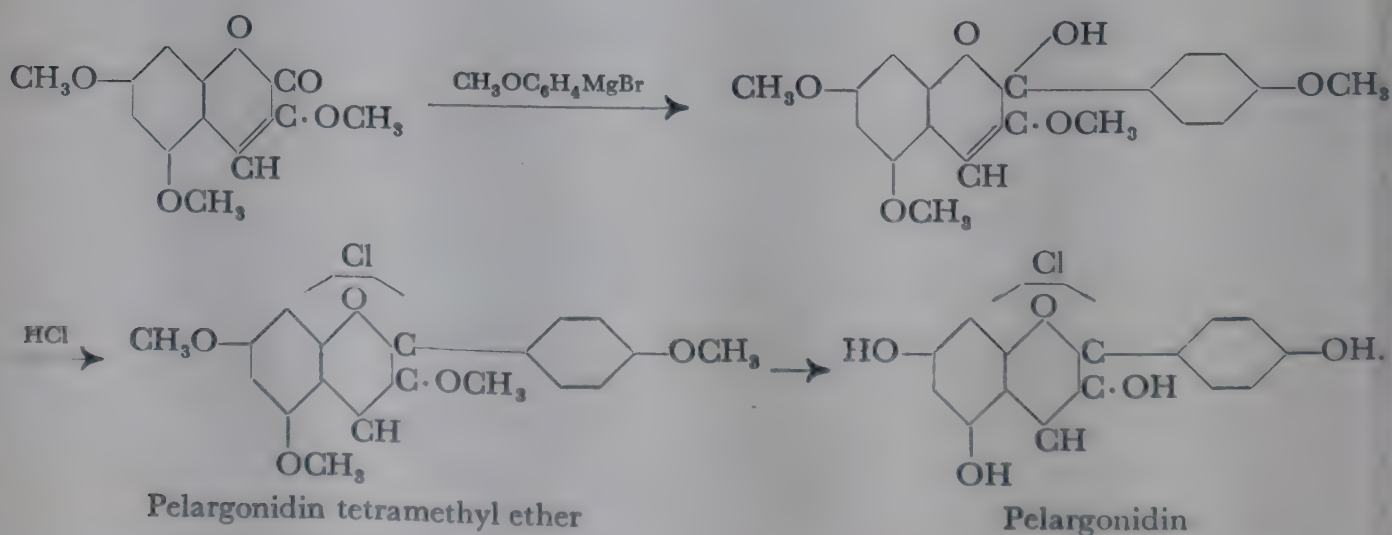


The cyclamen flower also contains a syringidin monoglucoside, *cyclamin*, which is probably identical with *œnin*.

For the determination of the constitution of these methylated anthocyanins, the alkali fusion is too drastic, since it is accompanied by extensive demethylation. On the other hand these anthocyanidins can be hydrolysed with boiling dilute solutions of sodium hydroxide or baryta water. From *pæonidin*, vanillic acid, and from *syringidin*, syringic acid are obtained in addition to phloroglucinol.

Many flower and berry pigments are difficultly separable mixtures of various anthocyanins. Thus, whortleberries contain monoglycosides of syringidin and delphinidin, as does also the black mallow (*Althæa rosea*). Also, the colouring matters of the blue grape and ampelopsis berries contain glycosides of syringidin and smaller amounts of glycosides of delphinidin.

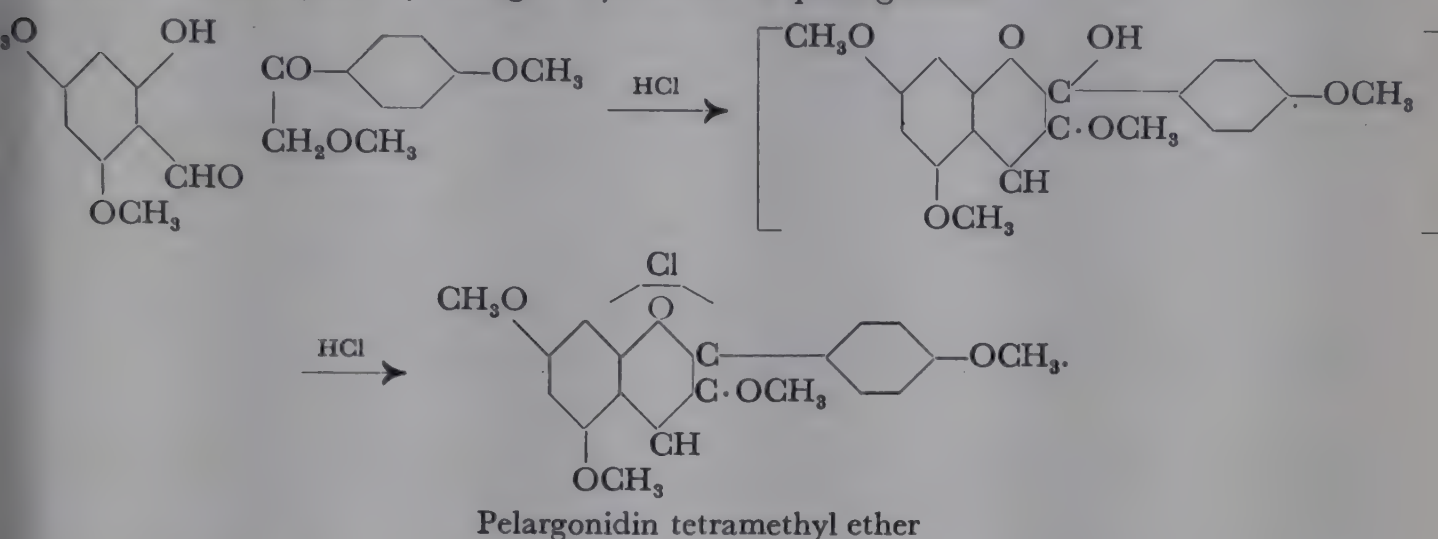
Pelargonidin, cyanidin, delphinidin, apigenidin and their various methyl



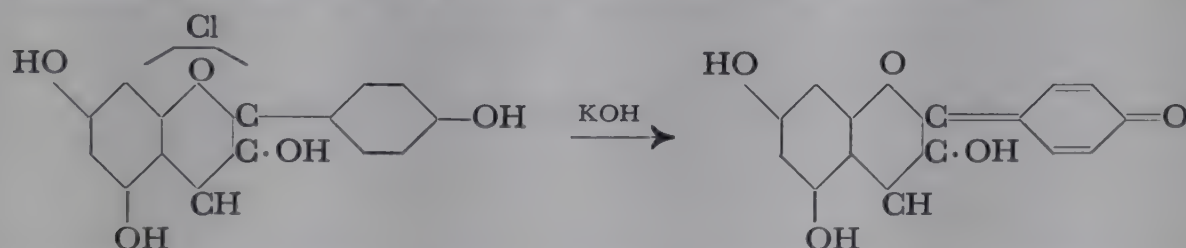
ethers have been prepared synthetically by two different methods. The principles of them will be shown by the synthesis of pelargonidin by the two methods:

(a) Willstätter's synthesis. *p*-Anisylmagnesium bromide reacts with 3:5:7-trimethoxycoumarin. The carbinol base of pelargonidin tetramethyl ether is thus formed, which, on acidifying, gives the chloride of pelargonidin tetramethyl ether. If the latter is heated with concentrated hydrochloric acid in a sealed tube, pelargonidin chloride is formed, the methoxy groups being hydrolysed off (see previous page).

(b) Robinson's synthesis. Phloroglucinaldehyde dimethyl ether, and *p*-methoxy- ω -methoxyacetophenone condense if hydrogen chloride is passed into their solution in glacial acetic acid. They form pelargonidin tetramethyl ether, which is hydrolysed by halogen hydric acids to pelargonidin:



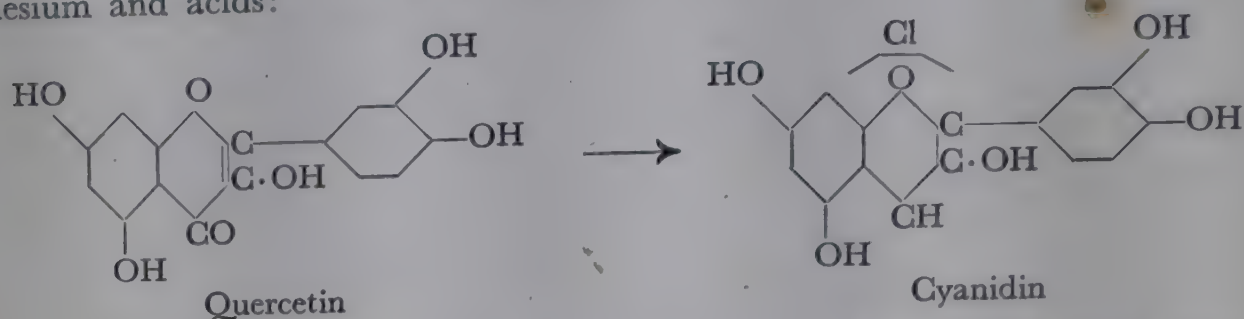
The salts of the anthocyanidins with acids all have a more or less red colour; pelargonidin, a yellowish red, cyanidin, red tinged with violet, delphinidin, blue-red. The free anthocyanidins, which are formed from the salts by the addition of the calculated amount of alkali, and which very probably have a quinonoid structure in the benzene nucleus (I. M. Heilbron):



are violet to blue; the alkali salts of the anthocyanidins, phenates, are blue. A good deal of the variation of the colours of flowers is due to the fact that the pigment is in some in a more acid, in others in a neutral or alkaline medium. This explains why, for example, the pigments of the red rose and the blue cornflower are identical. The rose contains salts of cyanin, whilst in the cornflower there are metal salts (probably chiefly potassium salts, together with some ammonium, calcium, and sodium salts). However, other factors besides this must be taken into account in explaining the varying shades of flowers. Among these factors are mixing of different anthocyanins, mixing with yellow pigments of the flavone and flavonol series, combination with tannins, which can often be detected in flowers, or with other substances ("co-pigments") which markedly alter the colour of the anthocyanin solutions.

All natural anthocyanins contain a sugar radical at the hydroxyl in position 3 of the pigment molecule. In the diglycosidic pigments the two sugar radicals can be attached at different OH-groups, or in the form of a diglycosidic group at the hydroxyl group 3. R. Robinson has prepared many of these natural products synthetically.

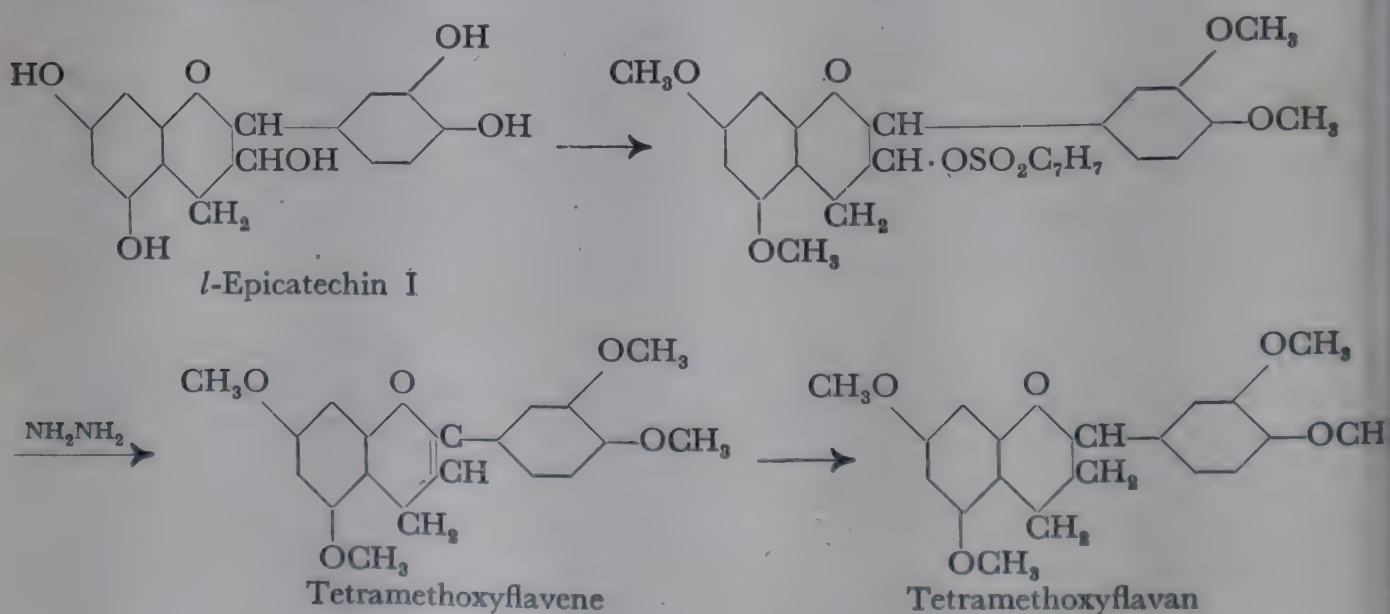
The close relationship between the anthocyanidins and the flavonols is obvious from their formulæ. It is very probable that plants are capable of converting the two groups of pigments one into the other by processes of reduction or oxidation. Such reactions can also be brought about *in vitro*. Quercetin can be reduced to cyanidin (though in poor yield, about 20%) by treatment with magnesium and acids:



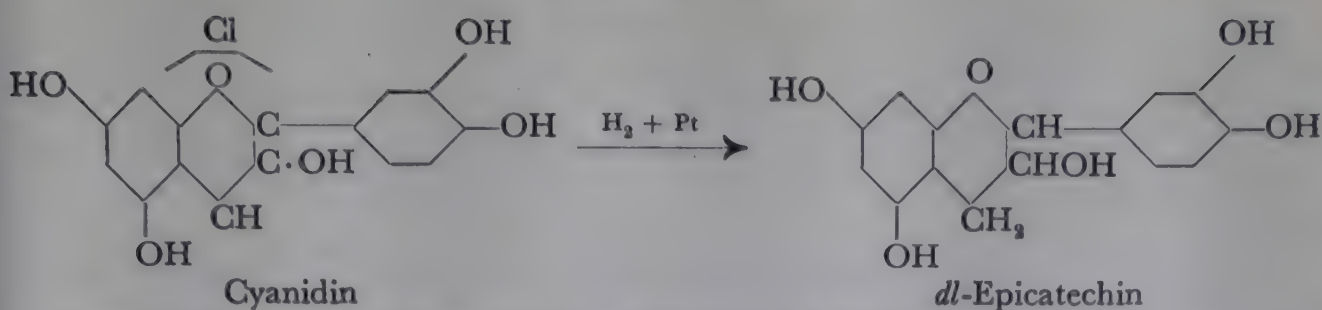
To these compounds belonging to the pyrone and pyrylium series, must be added a third group of vegetable substances, the catechins.

Catechins. A large number of plants contain crystalline, colourless compounds, which, as the work of Freudenberg showed, are to be regarded as hydrogenated flavonols or hydrogenated anthocyanidins; they are, on the other hand, parent substances of many natural tannins.

l-EPICATECHIN from *Acacia catechu* is a pentahydroxy-derivative of flavan. It has the constitution I. It can be converted into tetramethoxyflavan by the reactions shown below:



Of particular importance in connection with the determination of the structure of this substance is the fact that the pentamethyl ether of cyanidin can be reduced to *dl*-epicatechin pentamethyl ether with hydrogen and platinum, and cyanidin itself can be reduced to *dl*-epicatechin.



There is thus a very close constitutional, and indeed also genetic, connection between the catechins and the tannins derived from them (see p. 545), and the anthocyanins and flavonols. It is also possible to bring about the reverse change of catechin into cyanidin by an indirect method. If *d*-catechin tetramethyl ether is brominated in dioxane solution, bromocyanidin tetramethyl ether bromide is formed, which can be converted into cyanidin by the action of hydrogen iodide and phosphorus.

l-Epicatechin melts at 245°, and is optically active; $[\alpha]_{H_g} = -68^\circ$ (alcoholic solution) yellow

d-CATECHIN from *Uncaria gambir* appears to be a diastereoisomeride of *l*-epicatechin. It melts at 174–175°; $[\alpha]_{H_g \text{ yellow}} = +16.9^\circ$ (acetone solution). In alcohol no rotation of the plane of polarized light is observed.

It is possible to convert *dl*-epicatechin into *dl*-catechin, so that the synthesis of the latter also is thereby achieved.

The so-called *tea-catechin II*, or *gallocatechin*, has been isolated from green tea. It differs from epicatechin in containing an additional OH group (in the 5' position). It therefore stands in the same relationship to the anthocyanin pigment delphinidin as epicatechin does to cyanidin. It melts at 218° (Tsuji-mura). *l*-Epicatechin and *l*-epicatechin 3-gallic acid ester are also regular constituents of tea leaves. T.R.S.

The catechins are very probably the parent substances of the extraordinarily widely occurring group of amorphous and colloidal phloroglucinol tannins, and their tannin reds (phlobaphen). If catechin is heated in aqueous solution, it is soon converted into a colloidal tannin, whilst hot mineral acids produce an amorphous, quite insoluble precipitate, a so-called tannin red. Amorphous tannins and tannin reds of this kind are contained in catechu, Gambier catechu, and many other commercial drugs (see p. 547).

CHAPTER 44. INDIGO DYES ¹

Indigo

A series of plants indigenous to Eastern Asia, such as the *Indigofera* (*I. tinctoria*, *I. leptostachya*, *I. añil*, etc.), as well as dyer's woad (*Isatis tinctoria*), which was formerly cultivated in France and Germany, and *Polygonum tinctorium*, or dyer's knotgrass, contain the glucoside *indican*, $C_{14}H_{17}O_6N \cdot 3H_2O$, which, on hydrolysis with acids or enzymes breaks down into glucose and indoxyl, C_8H_7NO . The latter is immediately oxidized by atmospheric oxygen to *indigotin* (indigo blue, indigo).

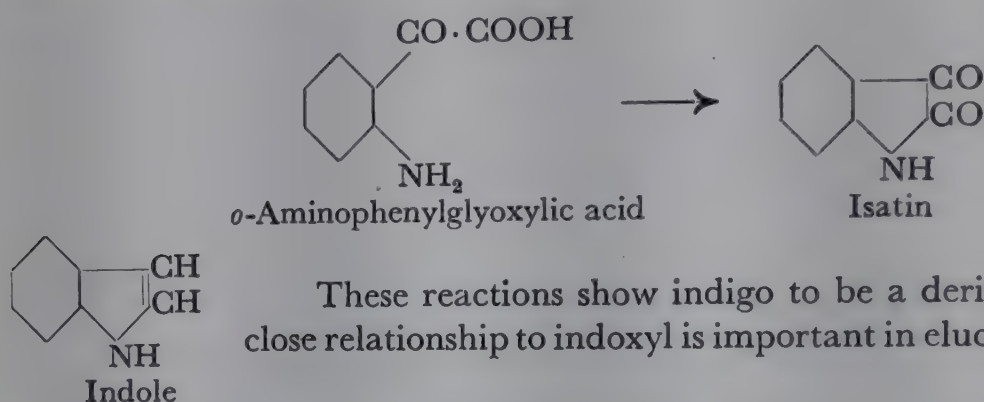
¹ See EDWARD THORPE, *Vat Dyes*, Leipzig and London, (1922). — J. MARTINET, *Matières colorantes, Les indigoides*, Paris, (1934). — A. V. BAEYER, *Gesammelte Werke*, Bd. I, *Über Indigo*, Brunswick, (1905).

Natural indigo was formerly prepared in this way from species of *Indigofera*, and partly from woad. It is the most important and the oldest of vegetable dyes. Besides the chief constituent, *indigotin* (20–95%), there are varying quantities of two other dyes, *indigo red* (indirubin) and *indigo brown*, along with ash and “*indigo gluten*”.

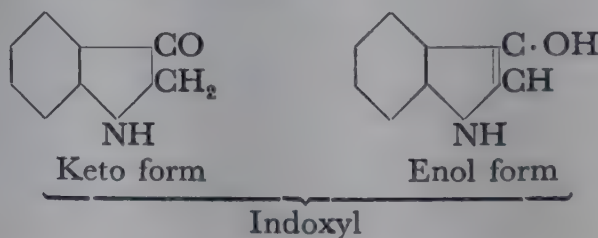
At present the larger part of the indigo consumption is supplied by the synthetic product which consists of pure indigotin.

The elucidation of the constitution of indigo, and the first syntheses of the dye, technically useless, however, were due to A. v. Baeyer. The industrially important methods are due to Heumann.

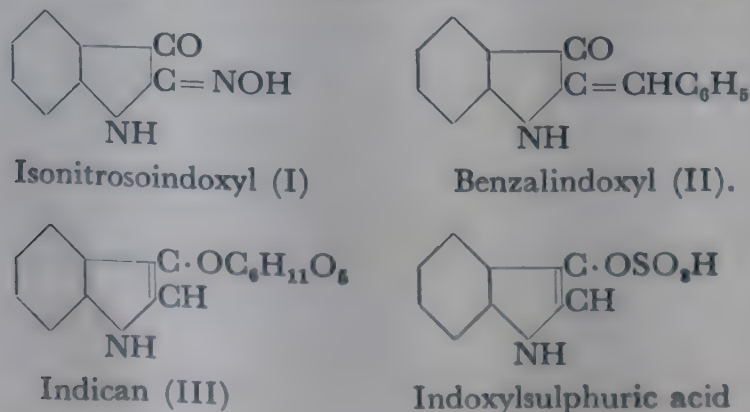
Indigotin, $C_{16}H_{16}N_2O_2$, is degraded by oxidizing agents (chromic acid, nitric acid) to isatin, $C_8H_5NO_2$. The structure of the latter compound is determined on the one hand by its conversion into indole, which will be described in Ch. 59, and on the other hand by a simple synthesis, consisting in the elimination of water from *o*-aminophenylglyoxylic acid:



The latter compound, for which different syntheses are available (see below), is capable of reacting in two tautomeric forms:

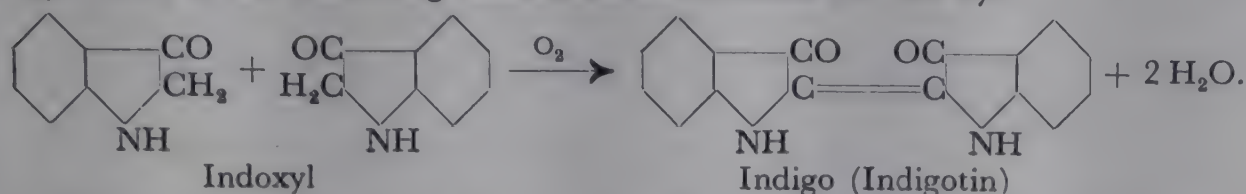


An isonitroso-derivative (I) and a benzal-compound (II), for example, are derived from the first form, whilst the glucoside, indican (III), from species of *Indigofera*, is to be regarded as a derivative of the enol form. The enol form of indoxyl is also found in indoxylsulphuric acid, a degradation product of tryptophan, which is formed in the animal organism and excreted by it:



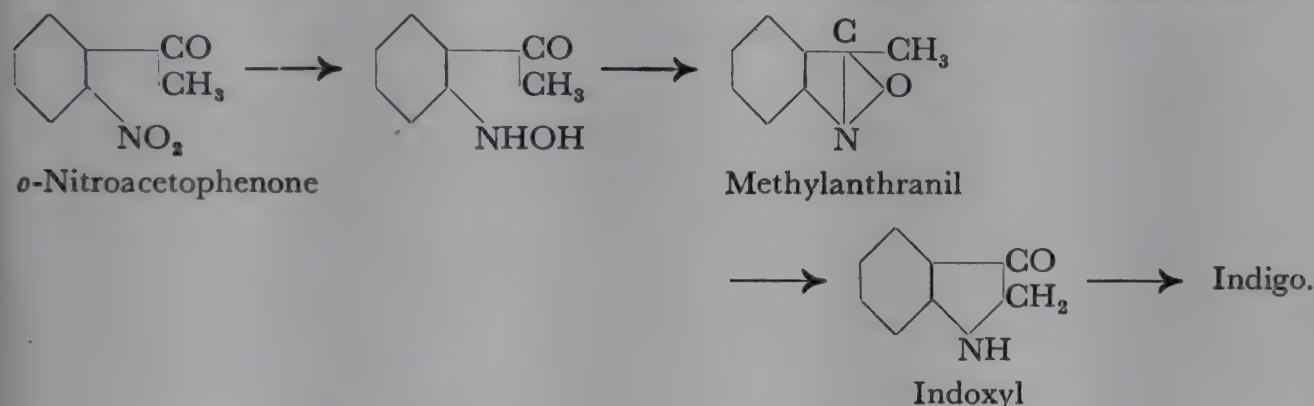
Indoxyl forms yellow crystals, which melt at 85° , and easily resinify. It dissolves in water with a yellow-green fluorescence. Its alcoholic solution gives a red colour with ferric chloride. The phenol-like enol structure of indoxyl is supported by its great solubility in alkalis.

The most important property of the compound is the ease with which it is oxidized, especially in alkaline solution. It loses two atoms of hydrogen, and two indoxyl-radicals condense to form a new molecule, indigotin. This synthesis of indigo leads to the following constitutional formula for the dye:



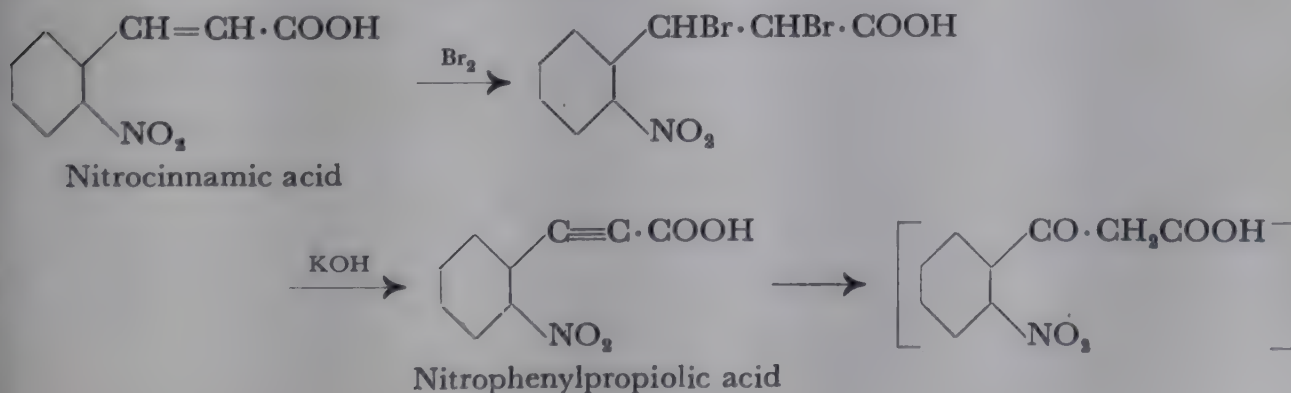
The problem of finding a technically efficient synthesis of indigo thus depends on discovering a convenient method of preparing indoxyl.

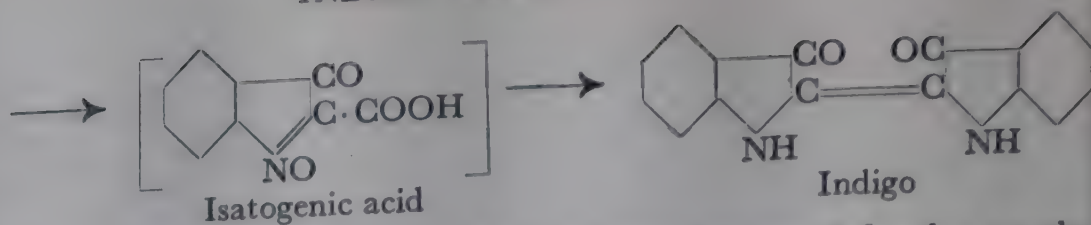
SYNTHESES OF INDIGO. Engler and Emmerling were the first to prepare indigo synthetically. They obtained the dye in very small quantities by the distillation of *o*-nitroacetophenone with zinc dust and soda-lime. The hydroxylamine derivative formed from the nitro-compound and methylantranil are intermediate products in this reaction. The latter rearranges to indoxyl on strong heating:



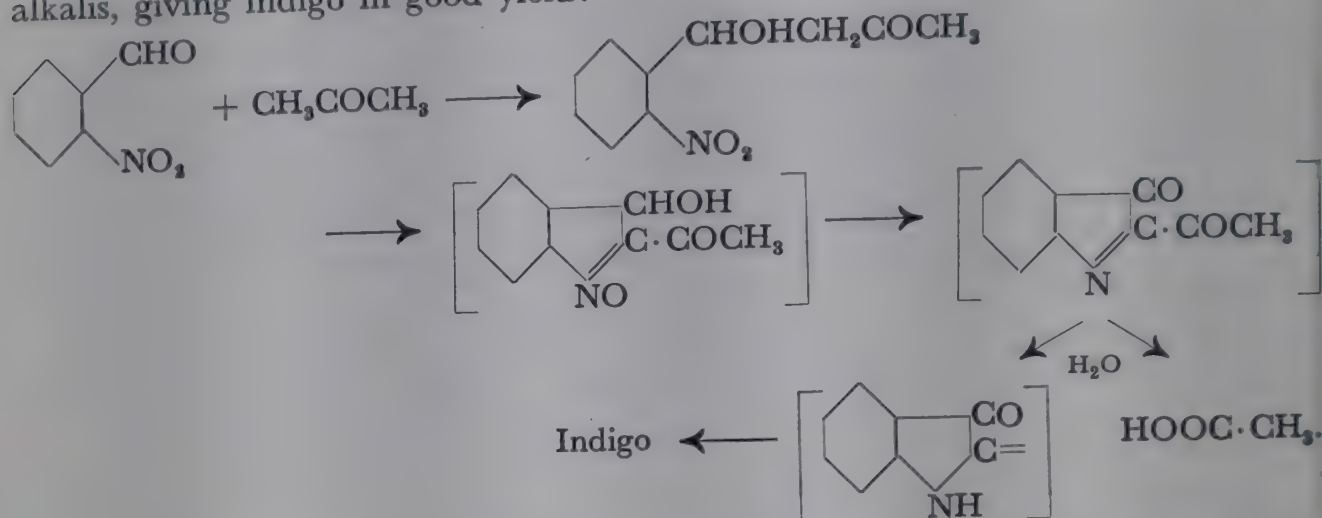
Later Nencki obtained indigotin by oxidation of indole. Attempts were also made to develop this process industrially, since indole occurs in considerable amounts in coal-tar, but they did not succeed.

Baeyer succeeded in synthesizing indigo by converting isatin into isatin chloride (see Ch. 59) by means of phosphorus pentachloride, and then reducing it. Two other methods also devised by Baeyer, are more important. The one starts with *ortho*-nitrophenylpropionic acid, which is obtained from *o*-nitrocinnamic acid. If this is boiled with alkali and reducing agents it is converted into indigo, probably by way of the so-called isatogenic acid:



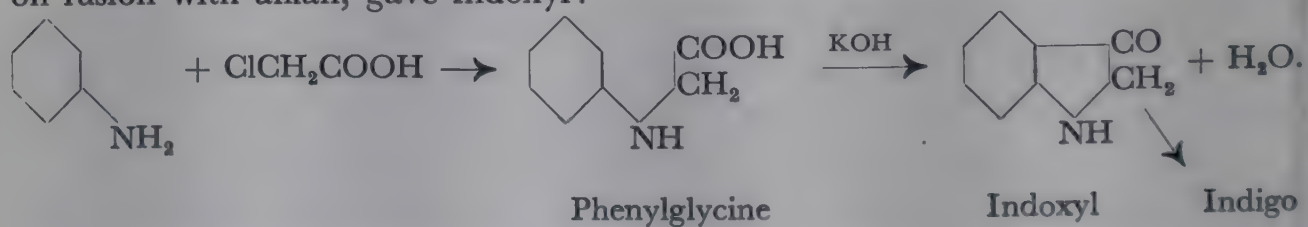


This process was used for a short time for the production of the dye on the fibre, but it did not hold its ground. The same happened with the following synthesis which originated in Baeyer's laboratory and which was likewise used for a short time in industry. *o*-Nitrobenzaldehyde was condensed with acetone and alkali to *o*-nitrophenyllactyl methyl ketone, and this was heated with caustic alkalis, giving indigo in good yield:



The technical indigo syntheses which have made the dye available so cheaply that the synthetic product not only competes with, but has largely displaced the natural substance, go back to Heumann. The processes have been developed in the industry.

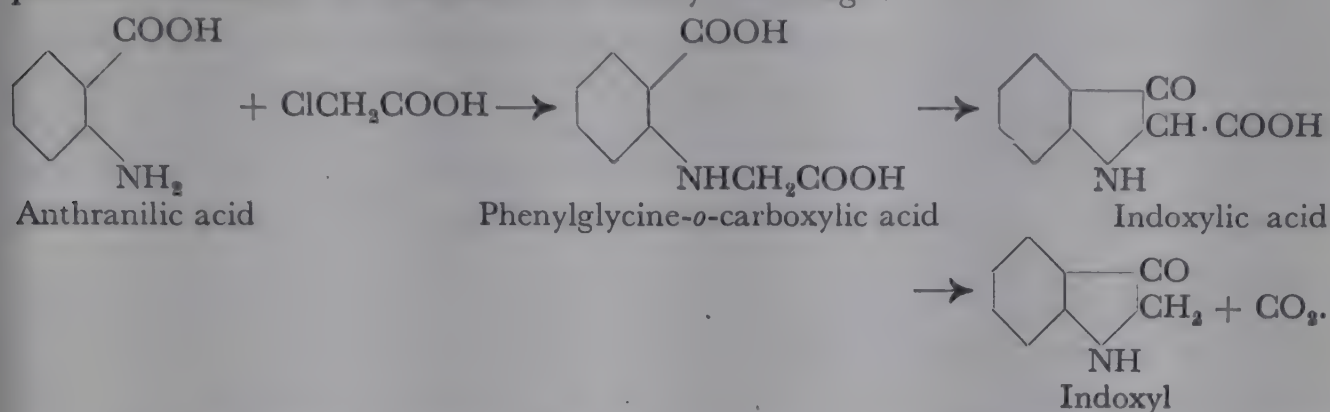
The *first Heumann synthesis* (1890) used aniline as the starting substance. This was made to react with chloracetic acid, giving phenylglycine, and this, on fusion with alkali, gave indoxyl:



With this method, however, the yield of the dye is small. The reason for this is, on the one hand, the high temperature of the alkali fusion, which leads to a partial decomposition of the indoxyl, and, on the other hand, the water produced in the reaction, which hydrolyses the phenylglycine. It was therefore, not only a decided advance, but a decisive factor for the technical use of the process, when Pfleger of the Deutsche Gold und Silberscheideanstalt introduced sodamide as the condensing agent in place of alkali. This allowed the phenylglycine fusion to take place even at 180–200°, and at the same time removed the water produced in the reaction, which combined with the sodamide to give ammonia and sodium hydroxide. The main part of synthetic indigotin is to-day manufactured by this modified process (in practice, a mixture of NaNH_2 , NaOH , and KOH is generally employed as the condensing agent).

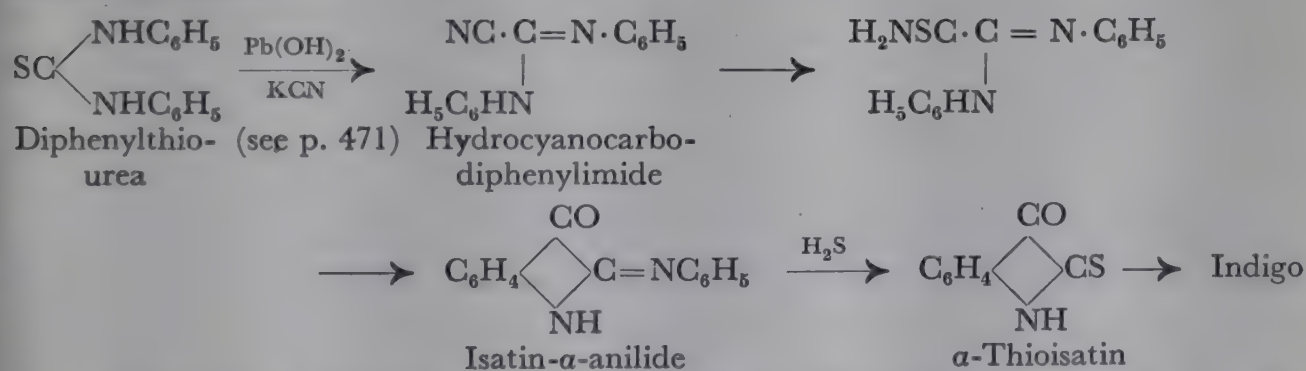
The second indigo synthesis which has been used for some time on a technical

scale is also due originally to Heumann, and was later improved in the Badische Anilin- und Sodafabrik. The starting material for this is anthranilic acid, which can be obtained cheaply from naphthalene, through phthalic acid and phthalimide (see p. 529). It is condensed with chloracetic acid to phenylglycine-*o*-carboxylic acid, and this is fused with alkali. Indoxylic acid is thus formed quantitatively, and this gives indoxyl with loss of carbon dioxide. The last stage in the process consists in the oxidation of indoxyl to indigo:



The Sandmeyer synthesis of indigo is based on totally different considerations. It starts with aniline and carbon disulphide. Diphenylthiourea (thiocarbanilide) is first obtained, and this is heated with white lead and potassium cyanide giving hydrocyanocarbodiphenylimide. Ammonium sulphide combines with the latter to give a thioamide, which gives, on treatment with concentrated sulphuric acid, isatin- α -anilide.

Isatin- α -anilide may be transformed on the one hand into isatin, and on the other into indigo. To convert it into indigo it may be reduced directly with ammonium sulphide, or, more conveniently, the isatin- α -anilide is first treated with hydrogen sulphide to give α -thioisatin, and this is converted into indigo by means of alkali:



Sandmeyer's synthesis is too expensive for the technical production of indigo, although most of its stages give practically quantitative yields, and the dye was produced for a time by this method. On the other hand, it is suitable for the manufacture of isatin- α -anilide, α -thioisatin, and derivatives of indigo.

Synthetic indigo has almost entirely superseded the natural product. The indigo cultivated in India is now only a small fraction of that grown formerly. In 1895–96 the export of the dye from India was 18,700 tons, whilst by 1913–14 it had decreased to about 1,100 tons. In the years of the Great War there was a larger amount exported, amounting to about 4,200 tons in 1915–16. This was because it was difficult to obtain the synthetic product. In addition to its lower price, synthetic indigo has the advantage of greater uniformity and purity.

Indigotin is a dark blue powder; m.p. 390–392°. Its vapour is purple-red.

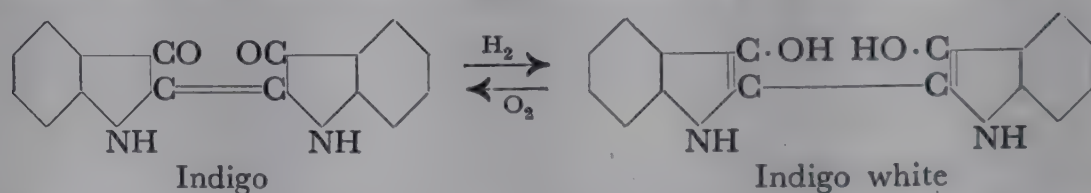
The dye is insoluble in water, alcohol, and ether, but it dissolves more or less readily in chloroform, nitrobenzene, aniline, etc. The colour of the solution usually appears blue, but in paraffin it is red. Theoretically speaking, a *cis*- and a *trans*-form may be anticipated for indigo, since it contains an ethylenic bond. The dye has the *trans*-configuration.

DYEING WITH INDIGO; VAT-DYEING. Indigo is the most important organic dye. It owes its importance to the excellent quality of the colour it produces, which is very fast to light, washing, alkali, and acid. The complete insolubility of the substance in water and alcohol, however, makes a special method of dyeing necessary. This is known as "*vat-dyeing*", and is used for many other dyes with similar physical and chemical properties to fix them on the fibre. Many "*vat-dyes*" are used at present in spite of their comparatively high price, on account of their fastness.

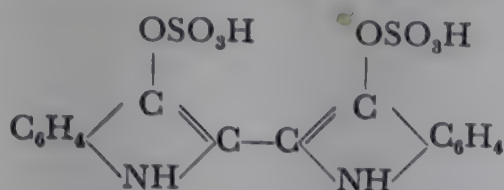
The principle of vat-dyeing is to reduce the water-insoluble dye to a derivative of phenolic nature, a so-called leuco-compound, which is soluble in alkali. This is almost always lighter in colour than the dye and frequently colourless. The fibre, e.g. cotton, is then steeped in the alkaline solution or suspension of the reduction product, the "*vat*", and is then exposed to the air. The oxygen re-oxidizes the leuco-compound on the fibre to the dye, and this adheres to the cotton, probably by adsorption forces, in the finely divided form in which it is produced.

The application of vat-dyeing is obviously limited to those dyes which can be easily reduced, and of which the leuco-compounds can be readily re-oxidized to the original dye.

Indigo shows this behaviour remarkably well. On reduction it takes up two hydrogen atoms and is converted into "*indigo white*", a substance which crystallizes in colourless leaflets. Atmospheric oxygen reconverts it quantitatively to the dye:

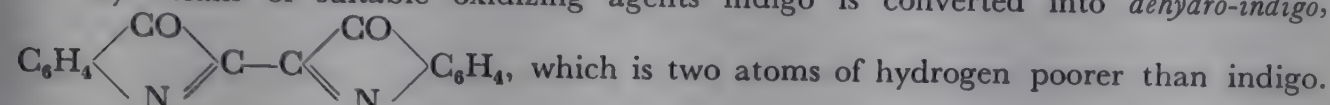


formed by the action of pyridine-sulphur trioxide on indigo white (and derivatives of indigo white), the sulphuric ester of indigo white being produced:



The sodium salt of this compound (indigosol O) is soluble in water, and is taken up from aqueous solution by wool and cotton. It can be converted into the indigo dye on the fibre by oxidation and elimination of the sulpho-groups. Similar "sols" are to-day also produced from other vat-dyes, provided that the latter contain easily reducible CO-groups.

By means of suitable oxidizing agents indigo is converted into *dehydro-indigo*,

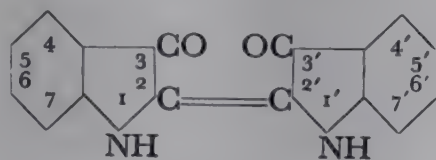


This is a dark yellow-red substance, which crystallizes well, and breaks down, readily on heating, into indigo on the one hand, and higher oxidation products on the other. It is an oxidizing agent.

Indigo derivatives. Indigoids.

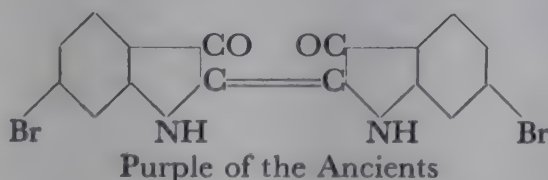
Amongst the simpler indigo derivatives, the halogenated indigos take a prominent place. They are distinguished by great fastness to chlorine, and give brilliant shades. The shade of the dye varies with the number and position of the chlorine atoms which enter the molecule.

Bromination of indigo in nitrobenzene leads successively to substitution in the 5:5'-, the 7:7'-, and finally the 4:4'-positions:



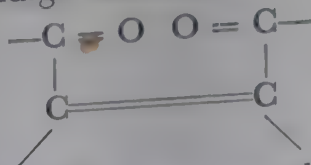
Ciba blue B is 5:7:5'-tribromoindigo, *ciba blue 2B* is 5:5':7:7'-tetrabromoindigo, *ciba blue G* or *indigo MLB 5B* consists of mixtures of tetra- and penta-bromoindigo. Hexabromoindigo and chlorinated indigos are also commercial products.

6:6'-Dibromoindigo occupies a special position. It has been shown by Friedländer to be identical with the pigment of the purple snail (*Murex brandaris*) known as *Purple of the Ancients* or *Tyrian purple*:



1.5 gm. of dye have been isolated from 12,000 purple snails. It was formerly used as a purple dye, but is now no longer employed for this purpose. Its shades are violet. Substitution by bromine in the indigo molecule in the 6:6'-positions thus causes a displacement of the shade of the dye towards the red.

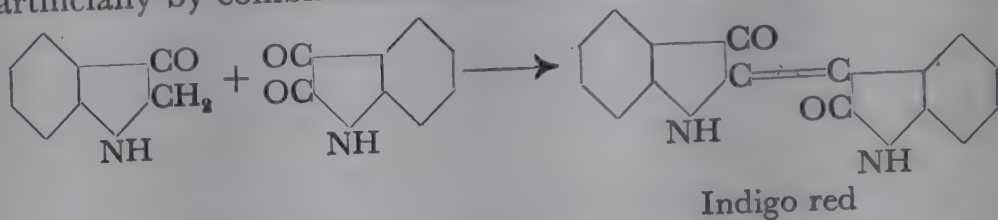
Thioindigo. Indigoids. The following grouping is regarded as being the chromophoric system of the indigo molecule:



It has been found that most compounds in which this chromophore occurs as a member of two ring systems, are coloured and often have dyeing properties. According to a proposal of Friedländer these dyes are called *indigoids*.

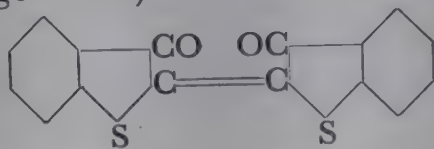
Those which contain the indoxyl radical $\text{C}_6\text{H}_4 \begin{array}{c} \text{CO} \\ \diagup \quad \diagdown \\ \text{C} \\ \diagdown \quad \diagup \\ \text{NH} \end{array}$, “indogen”, have been called *indogenides* by Baeyer.

The first indigoid dye to be mentioned is INDIGO RED. It is isomeric with indigotin, and accompanies it in natural crude indigo. The dye, which can be prepared artificially by combination of indoxyl and isatin, has no practical use:



The attempts of Friedländer to replace the two NH-groups of indigo by sulphur atoms have had great commercial consequences.

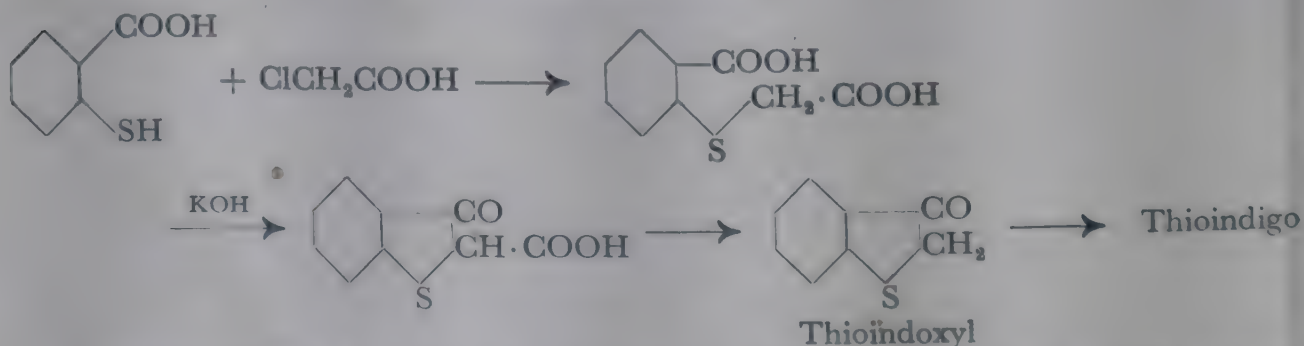
THIOINDIGO (thioindigo red B)



can be made in various ways, e.g. from thiosalicylic acid, which is first converted with chloroacetic acid into *o*-carboxyphenylthioglycolic acid. The latter gives, on fusion with alkali or sodamide, thioindoxylcarboxylic acid, and this, by loss of carbon dioxide gives thioindoxyl (3-hydroxy-1-thionaphthene). Thioindoxyl is very similar in its chemical behaviour to indoxyl, and can also be oxidized smoothly by atmospheric oxygen to thioindigo. (Thiosalicylic acid can be obtained, for example, from *o*-bromobenzoic acid and sodium disulphide, followed by reduction of the disulphide



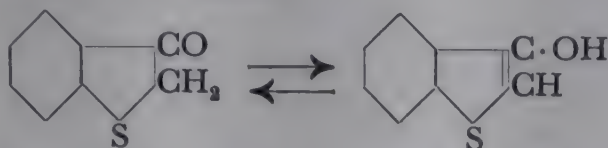
or from anthranilic acid *via* the diazo-compound).



Thioindigo red B (Ciba red) crystallizes in brown-red needles. It was the first pure red vat-dye. Its fastness to light and oxidation is greater than that of indigo.

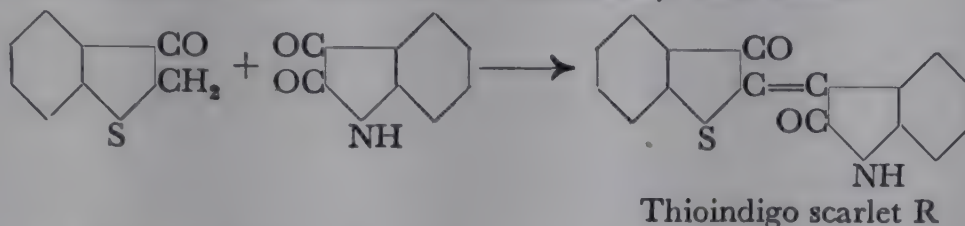
In the preparation of numerous substitution products of thioindigo (alkoxy-, halogeno-derivatives) it was observed that the regularity already noted in the indigo series, namely that substitution in the 6-position displaced the colour towards the yellow, and in the 5-position towards the blue, also held.

Thioindoxyl, or 3-hydroxy-1-thionaphthene, of which the tautomerism corresponds exactly to that of indoxyl:



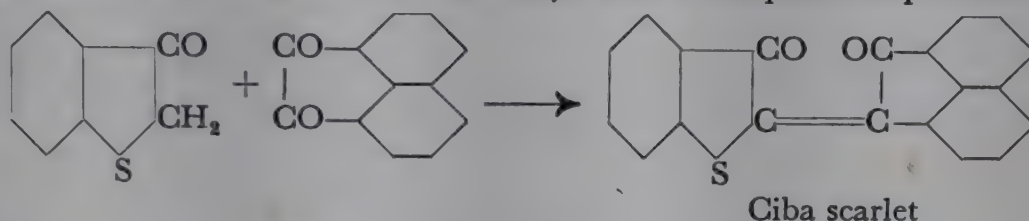
readily condenses with aldehydes and ketones. Amongst the indigoids thus produced are some technically very valuable dyes, such as:

THIOINDIGO SCARLET R, made from thioindoxyl and isatin:



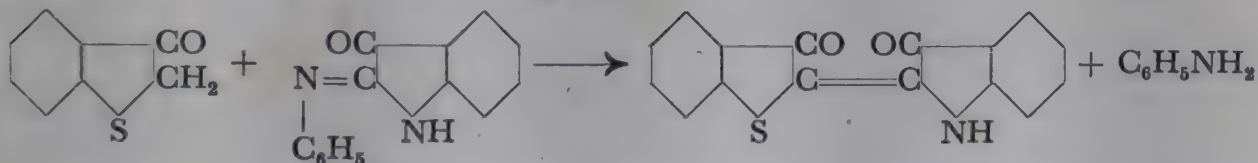
The colour is somewhat more yellowish than that of thioindigo.

CIBA SCARLET, made from thioindoxyl and acenaphthenequinone:



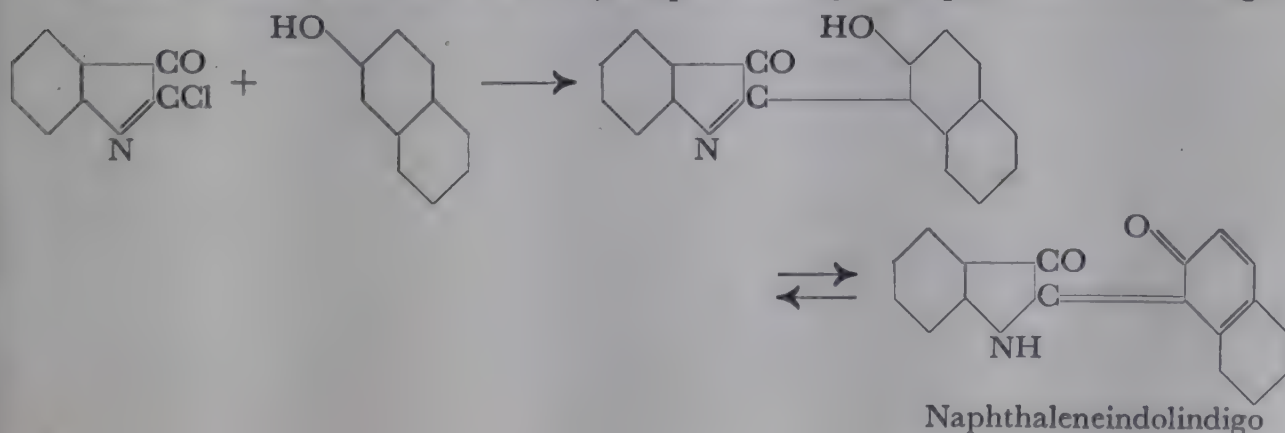
This dye is used commercially in spite of its high price, since its colour is outstandingly fast and pure.

Numerous indigoid dyes of unsymmetrical structure can be made from isatin- α -anilide or isatin chloride (Ch. 59) and thioindoxyl, phenols, naphthols, anthranols, etc. For example, thionaphtheneindolindigo is made from hydroxythionaphthene and isatin- α -anilide:



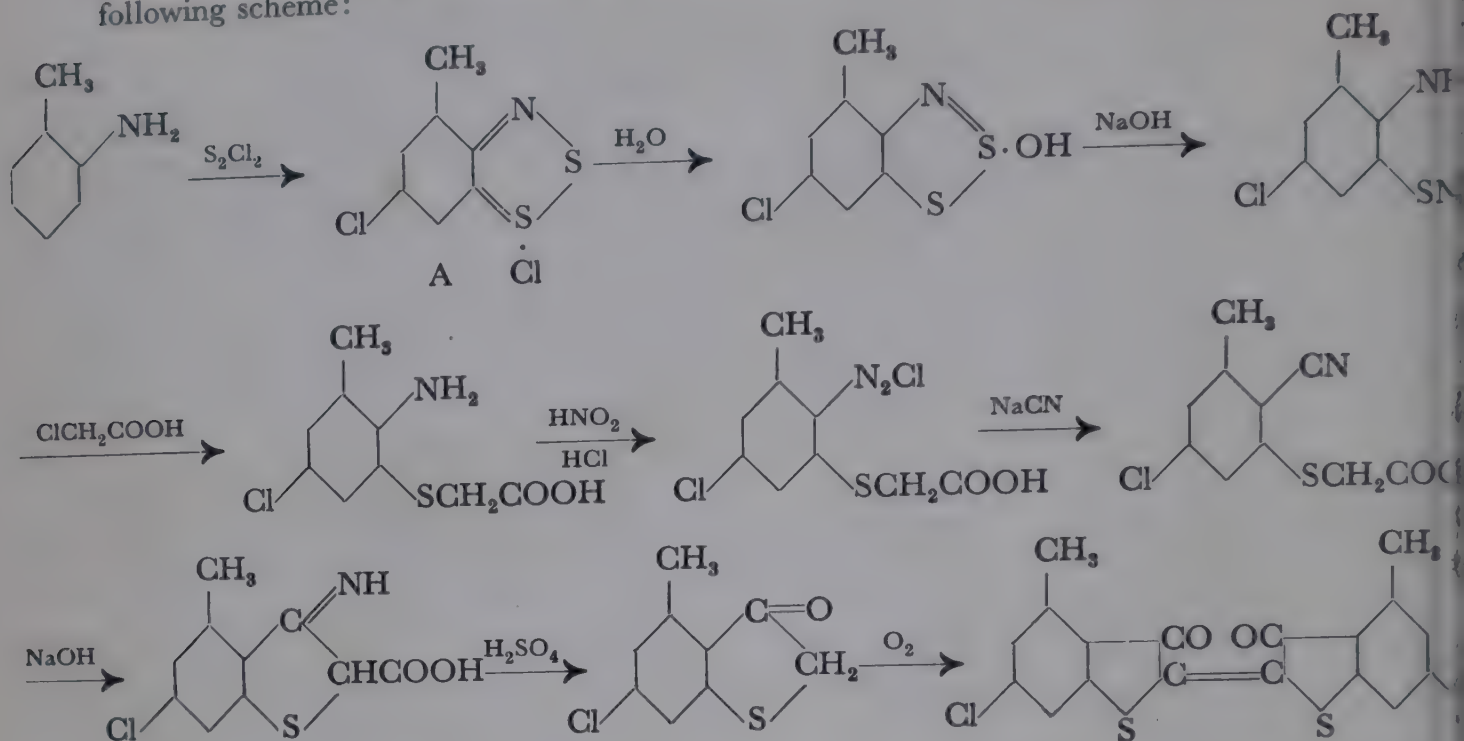
Brominated derivatives of this are the commercial dyes *Ciba violet B* and *3B*.

Isatin chloride condenses with β -naphthol to give naphthaleneindolindigo:



Alizarin-indigo 3R consists of bromo-derivatives of this compound.

For the preparation of *o*-mercaptans of aromatic amines, which are of considerable importance as starting products for the preparation of thioindigo derivatives and sulphur dyes, a method introduced by Herz is suitable, consisting in the action of S_2Cl_2 on the amine. First the thiazthionium chloride, A, is formed, and simultaneously chlorine enters in the *para*-position to the nitrogen. This intermediate product may then be further treated in various ways, being converted, for example, into thioindigo derivatives as shown in the following scheme:

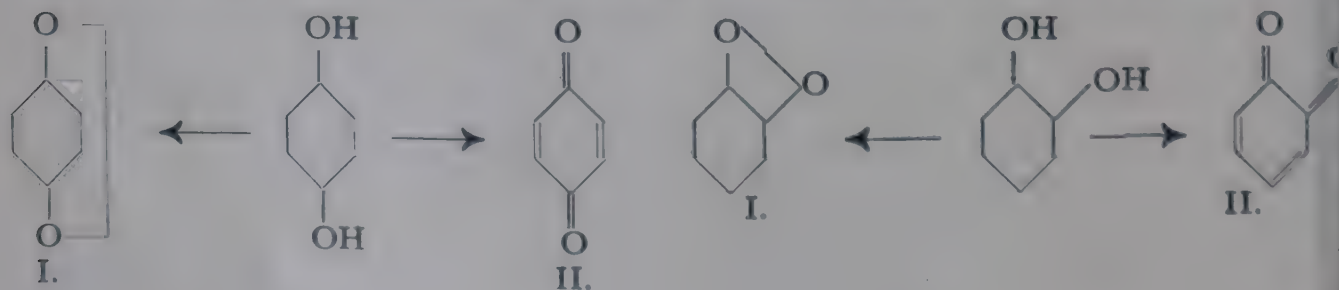


Section IV. Quinones

CHAPTER 45. BENZOQUINONES AND THEIR SIMPLER DERIVATIVES

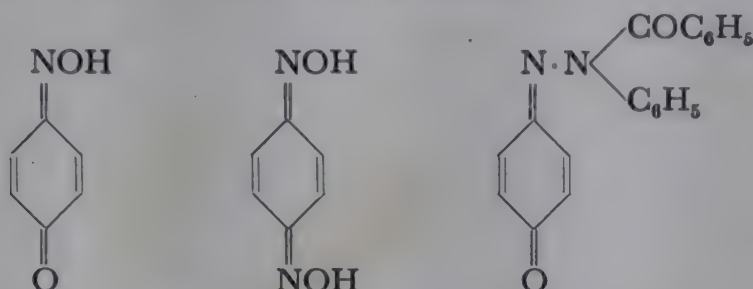
When hydroquinone, $C_6H_4(OH)_2$, is oxidized, it loses two hydrogen atoms and is converted into *p*-benzoquinone. In a similar way, oxidation of *o*-dihydroxybenzene under suitable conditions gives *o*-benzoquinone, which is two atoms of hydrogen poorer. *m*-Dihydroxybenzene, however, does not form a quinone.

The formulæ of the quinones must thus be derived from those of *o*- and *p*-dihydroxybenzene by the removal of two atoms of hydrogen. Maintaining the bivalency of oxygen the formulæ of the two quinones must be either I or II:

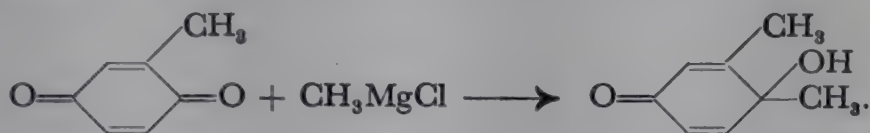


Actually the views on the structure of the quinones have varied from time to time between the two formulations, which may be called peroxidic and diketonic, respectively. At present *p*- and *o*-benzoquinone are commonly regarded as having the formulæ II, i.e. as being unsaturated diketones, for the following reasons:

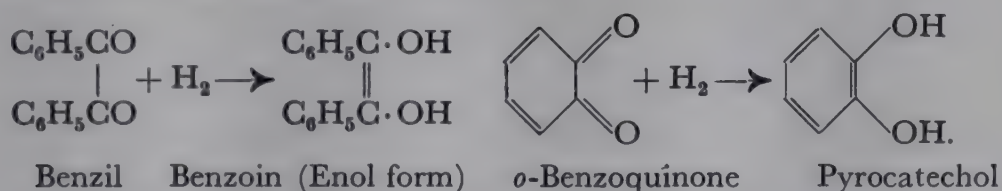
(a) Quinones show the reactions of the carbonyl group. *p*-Benzoquinone combines with hydroxylamine hydrochloride to form a monoxime and a dioxime, and with benzoyl-phenylhydrazine to give a hydrazone (primary hydrazines, e.g. phenylhydrazine itself, are oxidized by quinone):



(b) Alkylmagnesium salts react with quinones in the same way as they do with ketones. The reaction products are tertiary alcohols, *quinols*. However, the yield in the case of *p*-benzoquinone itself is very small, but is somewhat better for methylquinone:

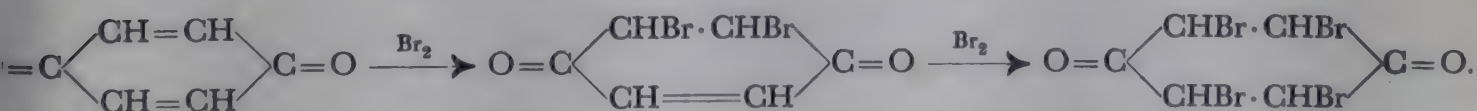


(c) Also the fact that the quinones are readily reduced to dihydroxybenzenes, a reaction which may be best compared with the reduction of benzil to benzoin, is in agreement with the diketonic structure:



The above-mentioned reactions give evidence particularly of the existence of carbonyl groups in the quinones. The following reactions indicate the presence of unsaturated carbon double bonds:

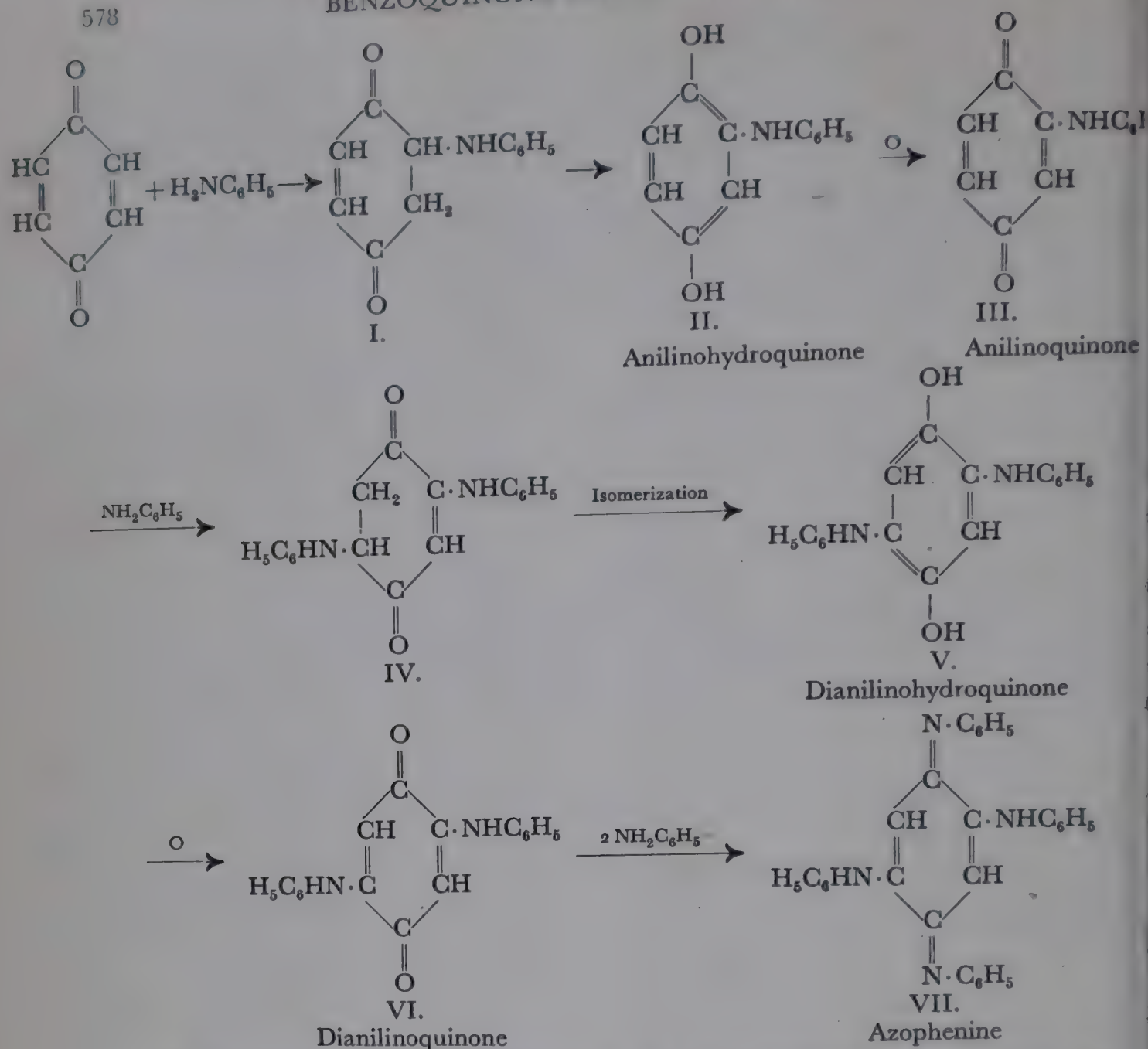
(d) *p*-Benzoquinone adds on successively two, then four atoms of bromine:



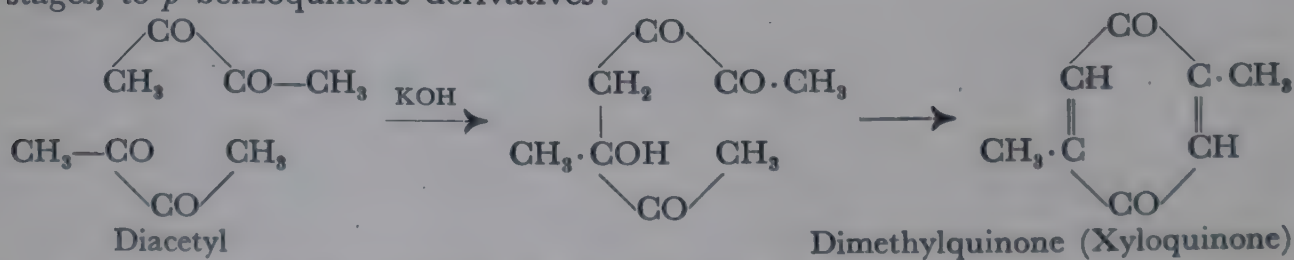
(e) Amines, such as aniline, for example, add on to quinone. The reaction product (I) isomerizes at once to anilinoquinone (II), which, after oxidation by atmospheric oxygen to the quinone derivative (III) takes up a second molecule of aniline, and is converted through (IV) to dianilinoquinone (V). Dianilinoquinone is oxidized by atmospheric oxygen to dianilinoquinone (VI). The latter exchanges its oxygen atoms for aniline groups and is converted into *dianilinoquinone dianil* or *azophenine* (VII), a dark-red substance, which crystallizes well (m.p. 240°):

BENZOQUINONE AND DERIVATIVES

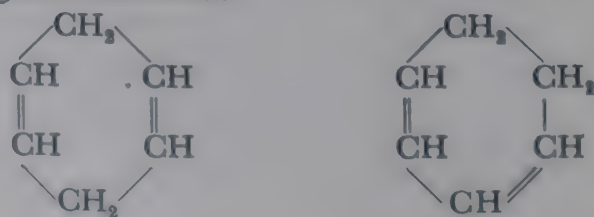
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(f) Finally, certain syntheses of quinones give evidence of the structure of these compounds, especially those starting with α -diketones. Diacetyl and related α -diketones condense under the action of alkalis, through aldol-like intermediate stages, to *p*-benzoquinone derivatives:



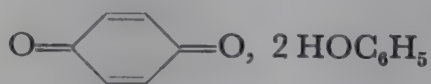
The quinones are therefore to be regarded as oxo-derivatives of unsaturated cyclic hydrocarbons; *p*-benzoquinone is derived from $\Delta^{1,4}$ -cyclohexadiene, and *o*-quinone from $\Delta^{1,3}$ -cyclohexadiene:



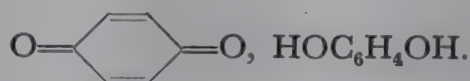
According to systematic principles, the quinones should be dealt with in Part II B of this book, among the alicyclic compounds. The extraordinarily close genetic relationships between them and the aromatic substances, makes it, however, more convenient to deal with them here. There are innumerable transitions between benzenoid and quinonoid substances, and in the case of some complex derivatives of the quinones (e.g. certain dyes) it is still contested whether a quinonoid or a benzenoid structure better represents their behaviour.

The simple quinones are yellow compounds, often volatile in steam. They often have a sharp smell reminiscent of chlorine. As they are easily reduced to dihydroxybenzenes they have oxidizing properties.

The oxidation of hydroquinone to *p*-benzoquinone proceeds through an interesting dark-green intermediate product, *quinhydrone*. This compound is also formed from equimolecular quantities of quinone and hydroquinone, and is, therefore, doubtless made up of these two components. As regards its constitution it is important to note that other quinhydrones, with completely analogous properties, can also be obtained from benzoquinone and phenol ("phenoquinone") and, similar aromatic hydroxycompounds:

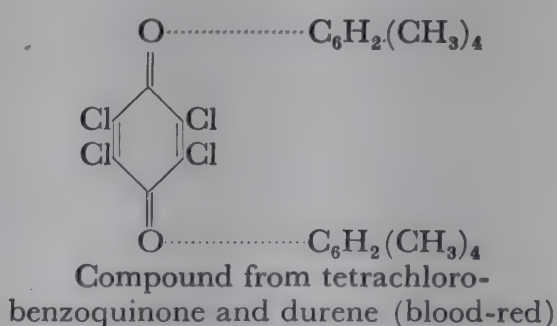
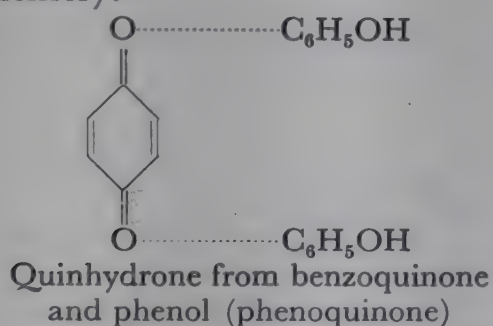


"Phenoquinone"



Quinhydrone

Their dark colour points to a strongly unsaturated nature. Quinhydrones are regarded as molecular compounds in which the residual affinity of the carbonyl groups of the quinone, on the one hand, and those of the aromatic (benzenoid) component on the other, have saturated each other. In confirmation of this view there is also the fact that a number of molecular compounds of quinones with aromatic amines, and of tetrachloroquinone and aromatic hydrocarbons (e.g. durene) are known, and also that isoprene and terpenes give coloured solutions with quinones, which appear to be due to the formation of addition products (P. Pfeiffer):

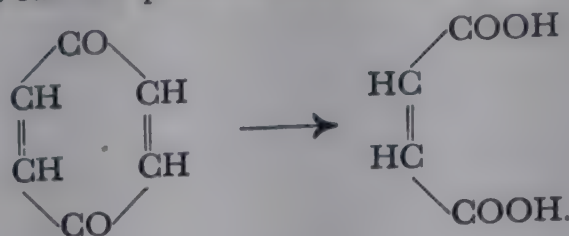


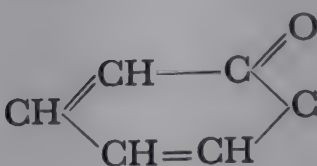
Individual quinones. *p*-BENZOQUINONE, $\text{O}=\text{C} \begin{array}{c} \text{CH}=\text{CH} \\ \text{CH}=\text{CH} \end{array} \text{C}=\text{O}$ was the

first quinone to be discovered. Woskresensky obtained it in 1838 by oxidation of quinic acid, from which its name quinone, is derived. The compound is yellow, is volatile in steam, possesses a strong, pungent smell, and colours the skin brown. It melts at 116°. As mentioned above, *p*-benzoquinone is formed by the oxidation of hydroquinone. Ordinarily, however, it is prepared from aniline, which, on treatment with potassium dichromate and sulphuric acid is oxidized, through

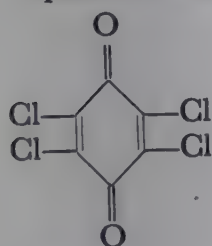
various oxidation stages (phenylquinonimines (see p. 583), aniline black (see p. 585)) to *p*-benzoquinone. It is used in tanning (quinone leather).

Potassium persulphate in the presence of silver sulphate brings about an important decomposition of quinone to maleic acid and some fumaric acid. This can be considered as a further proof of the structure of quinone:



o-BENZOQUINONE, , is formed by the oxidation of

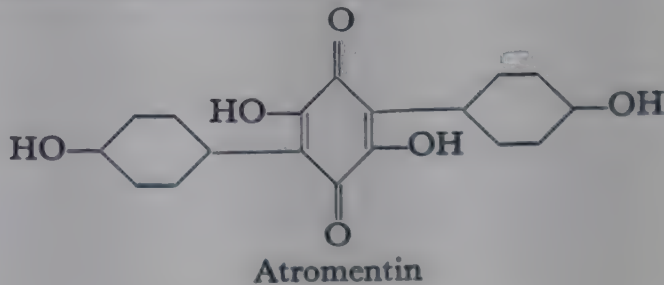
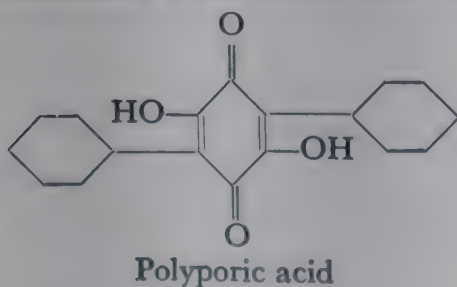
pyrocatechol in absolute ether solution with silver oxide (Willstätter). It forms red tablets, has no smell, is not volatile in steam, and is very unstable. In its preparation a second, colourless modification is often observed, which readily changes into the red form, with which it is probably dimorphous. A chlorinated *o*-quinone was discovered by Zincke earlier. More important is



TETRACHLORO-*p*-QUINONE, or CHLORANIL (Erdmann). This is formed from a large number of aromatic compounds, e.g. aniline, phenol, *p*-aminophenol, *p*-phenylenediamine, when heated for a long time with potassium chlorate and hydrochloric acid. *p*-Phenylenediamine is a suitable substance from which to prepare it. Chloranil crystallizes in yellow leaflets, which melt at 290°. It is

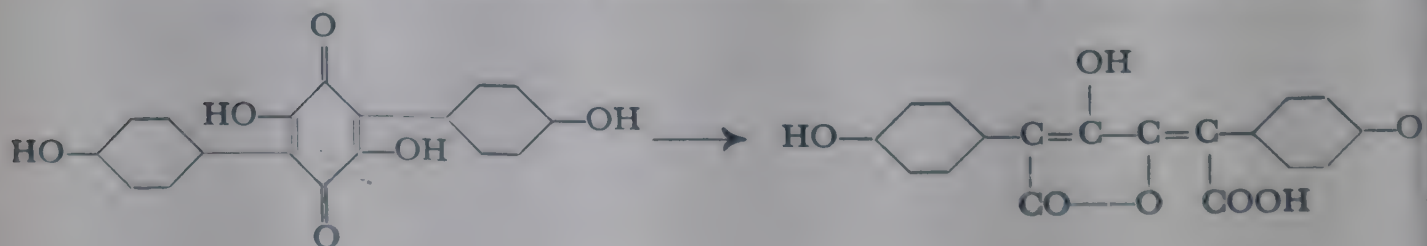
used as an oxidizing agent. When acted upon by chlorine it breaks down to give dichloromaleic acid.

The work of F. Kögl has shown that derivatives of 2:5-diphenyl-*p*-benzoquinone occur as pigments of certain fungi. Thus *polyporic acid* from a species of *Polyporus* is 2:5-diphenyl-3:6-dihydroxybenzoquinone, and *atromentin* from *Paxillus atrotomentosus* (a species of mushroom) is 2:5-[di-*p*-hydroxydiphenyl]-3:6-dihydroxybenzoquinone:



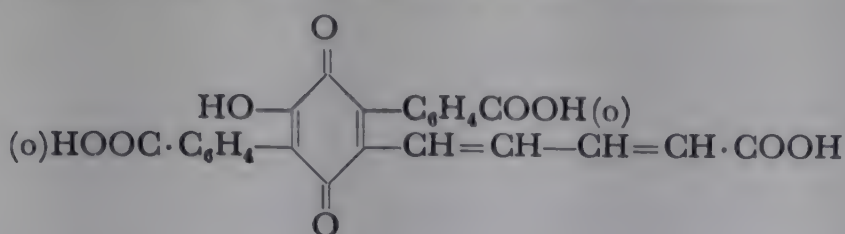
Both compounds can also be obtained synthetically.

Atromentin can be oxidized to atromentic acid, a vulpinic-pulvinic acid derivative:



This change is of interest, particularly from the biological point of view, since vulpinic acid and its derivatives are widely-occurring lichen dyes (see p. 528).

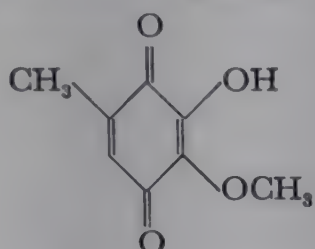
The red pigment of the fly agaric, *muscarufin*, has the formula:



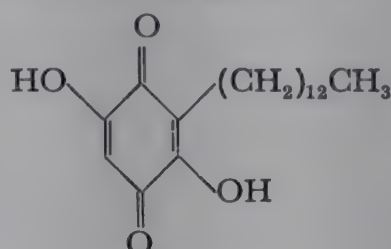
Distillation of the pigment with zinc dust gave *p*-diphenylbenzene, and oxidation with hydrogen peroxide gave phthalic acid. Also acetylation indicated the presence of one hydroxyl group, and hydrogenation and addition of maleic anhydride indicated the presence of the unsaturated side chain.

The amount of pigment obtained from 500 kg of the fungus was 0.85 gm.

Among the *p*-benzoquinone derivatives occurring in nature are also found *fumigatin* (3-hydroxy-4-methoxy-2:5-toluquinone), from *Aspergillus fumigatus* (H. Raistrick), and *rapanone*, the anthelmintic principle from *Rapanea Maxmowiczii* Koidz:

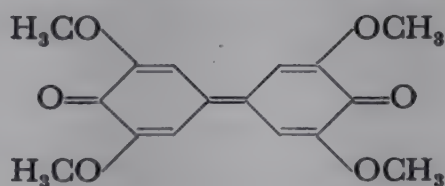


Fumigatin



Rapanone

DIPHENOQUINONE, $\text{O}=\text{C}_6\text{H}_4=\text{C}_6\text{H}_4=\text{O}$, a quinone of the biphenyl series, is obtained by oxidation of *p,p'*-dihydroxybiphenyl. It forms yellow needles. A tetramethoxy-derivative of this compound, *coerulignone*, or *cedrret*,



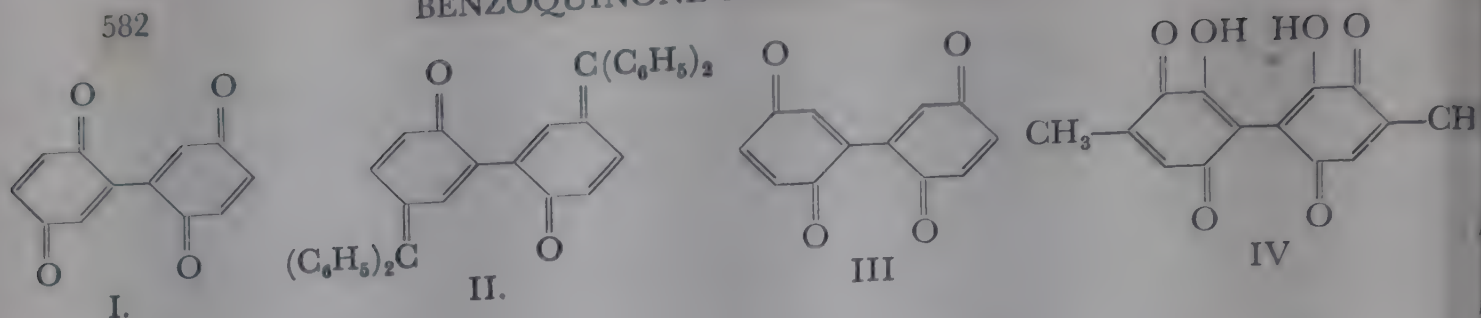
was first discovered during the purification of pyroligneous acid with chromic acid.

It is produced here by the oxidation of pyrogallol dimethyl ether, $\text{HO}-\text{C}_6\text{H}_2(\text{OCH}_3)_2$,

which occurs in beech and birch wood tar, and is therefore also present in small quantities in crude pyroligneous acid.

Crystals of coerulignone have a steel-blue colour. On reduction the substance takes up two atoms of hydrogen, and is converted into hydrocoerulignone, the tetramethoxy-derivative of *p,p'*-dihydroxybiphenyl. Coerulignone enters into addition reactions in the same way as the other quinones of the benzene series.

In addition to diphenoquinone, there are other quinones and also diquinones of the biphenyl series. Derivatives of a di-*para*-quinone (I), e.g. *difuchsonyl* (II) (Bistrzycki), are known. A derivative of di-*para*-quinone (III) is found as a pigment from *Penicillium phæniceum*, viz. *phœnicin* (IV):

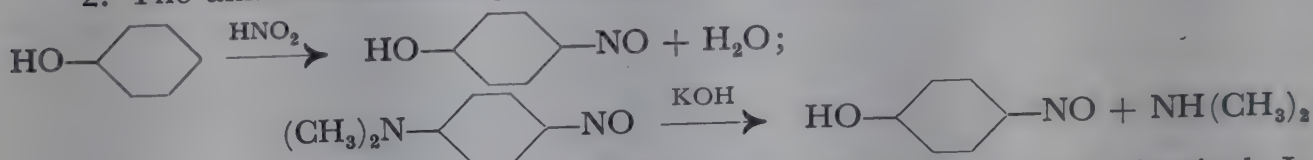


Derivatives of benzoquinones

A. Quinone oximes. Whilst *p*-benzoquinone oxidizes hydroxylamine in alkaline solution, it reacts with the mineral acid salts of this compound with the formation of quinone monoxime and quinone dioxime (formulae, p. 577).

Two other important methods are available for the preparation of *quinone monoxime*:

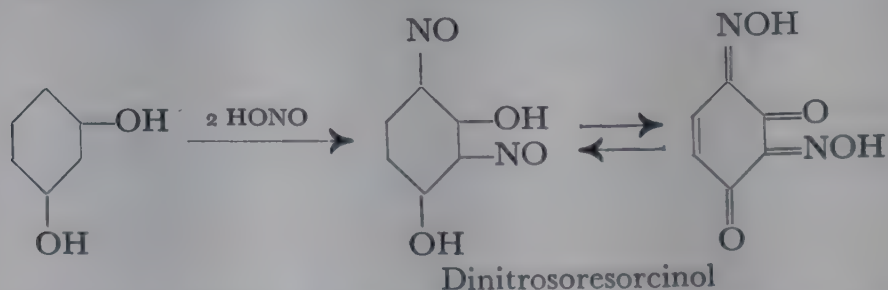
1. The action of nitrous acid on phenol, and
2. The alkaline fission of *p*-nitrosodimethylaniline:



The products obtained by the three different methods are all identical. It must therefore be concluded that the compound is desmotropic, and can therefore react either as quinone monoxime or as *p*-nitrosophenol. This establishes a new close relationship between benzenoid and quinonoid substances.

Benzoquinone oxime (*p* nitrosophenol) forms pale yellow needles, which dissolve in alcohol and ether with a green colour, and in alkalis with salt-formation with a brown colour. Its melting point is 126°. On oxidation with potassium ferricyanide it is converted into *p*-nitrophenol, and by reduction into *p*-aminophenol. Quinone dioxime is of little interest. It is yellow, and decomposes at about 240°.

The dioxime of di-*ortho*-benzoquinone is the so called *dinitrosoresorcinol*, obtained by the action of nitrous acid on resorcinol:



The compound is yellow. It forms a green lake with iron and dyes iron-mordanted cotton a green colour which is fast to washing and light. With a chrome mordant it dyes brown. It finds use as a dye under the name "chlorin", or "Solid green O".

B. Quinonimines. The quinonimines are derived from the quinones by replacement of the oxygen atoms by =NH groups:



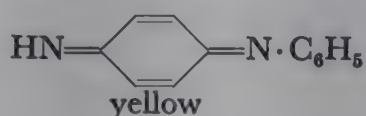
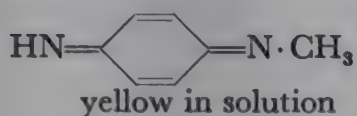
Quinonemonoimine is obtained from *p*-aminophenol, and *quinonediiimine* from *p*-phenylenediamine by oxidation with silver oxide.

Both compounds are *colourless* and very reactive. On warming with dilute sulphuric acid they are hydrolysed to quinone and ammonia. Instability towards mineral acids is a characteristic property of this class of substances. In common with the quinones they are readily reduced. Stannous chloride reduces quinonemonoimine to *p*-aminophenol, and the diimine to phenylenediamine.

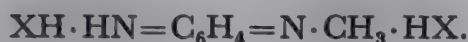
It is remarkable that the replacement of the hydrogen atoms of the imino-groups by alkyl or aryl radicals results in a considerable deepening of the colour. A light yellow N-methyl derivative, and a yellow-red N-phenyl derivative are derived from the colourless quinonemonoimine.



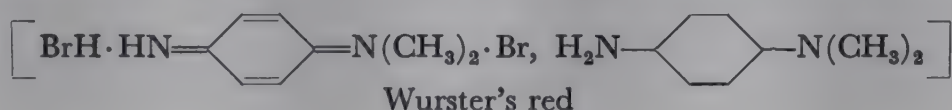
The substitution products of quinonediiimine are also coloured:



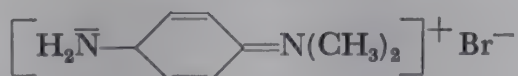
The salts of the quinoneimines, similar in type to ammonium salts, are called *imonium salts*, e.g. N-methylquinonediiimonium salts,



They are coloured. Some of them can combine with benzene derivatives to give quinhydrone-like, molecular compounds, in the same way as the quinones. One such product is "*Wurster's red*", which is formed by oxidation of an acid solution of *as*-dimethyl-*p*-phenylenediamine, and is made up of one molecule of dimethyl-*p*-phenylenediamine and one molecule of dimethylquinonediiimonium salt:

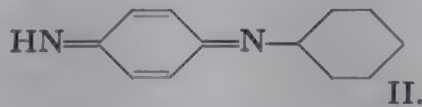
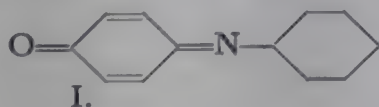


According to more recent views the compound is, however, not regarded as a quinhydrone, but as a "semiquinone radical", to which the following structure has been ascribed:



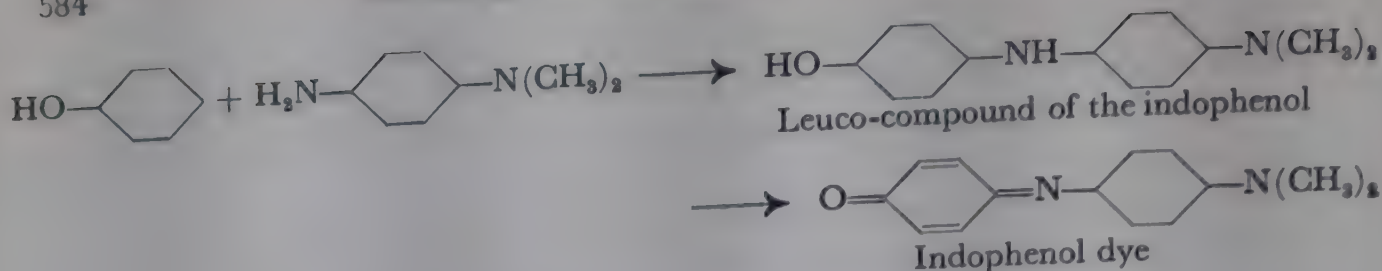
This view has been arrived at as a result of molecular-weight determinations (Weitz) and magnetometric measurements (Sugden).

C. Indophenols. Indamines. Amino-derivatives of phenylquinonemonoimine (I) are known as indophenols, and amino-derivatives of phenylquinone-diimine (II) are known as indamines:

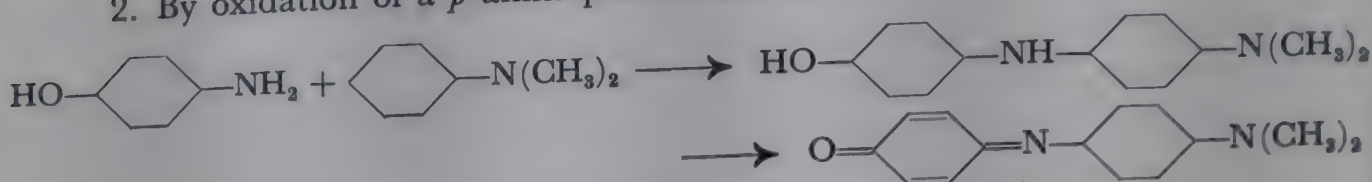


The *indophenols* are prepared:

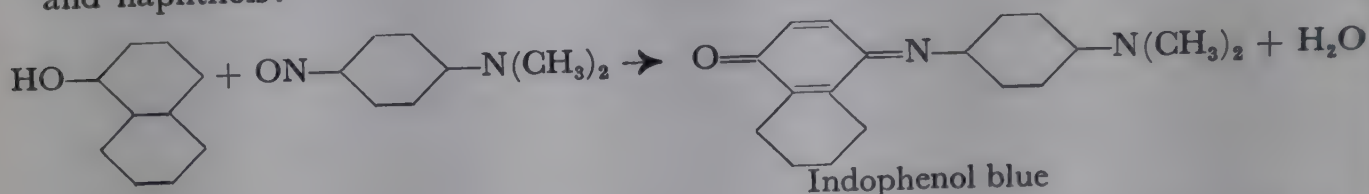
1. By oxidation of an equimolecular mixture of a phenol and a *p*-diamine, which contains at least *one* primary amino-group:



2. By oxidation of a *p*-aminophenol and an amine:



3. By condensation of *p*-nitroso-derivatives of tertiary bases with phenols and naphthols:

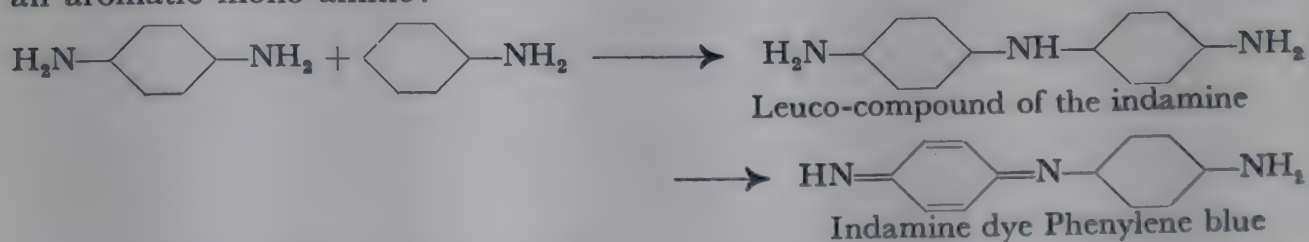


The indophenols are very easily decomposed by acids into a quinone and an amine. That is the reason why they are not more extensively used in the dyeing industry. The only indophenol which has been used commercially is the above-mentioned *Indophenol blue* or *α -Naphthol blue*. It was used in the same way as a vat-dye, i.e. it is brought on to the fibre in the form of the leuco-product, and the dye itself is regenerated on the fibre by the action of atmospheric oxygen. The indigo-blue shade obtained with Indophenol blue recalls that of indigo itself.

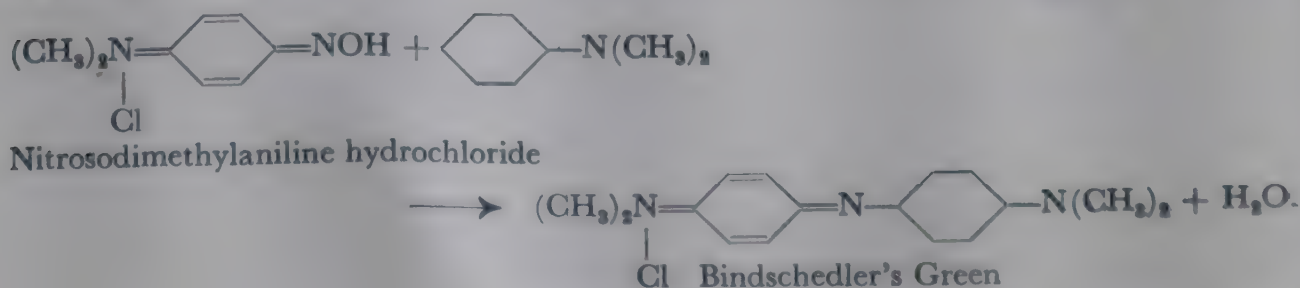
Large amounts of various indophenols are used commercially in the manufacture of sulphur dyes (see p. 626).

INDAMINES are obtained by processes analogous to those used for the indophenols, viz.

1. By oxidation of a *p*-diamine which has at least one free NH_2 -group, with an aromatic mono-amine:

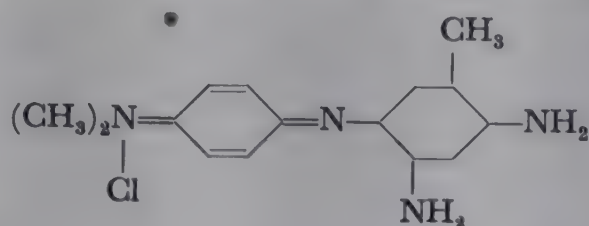


2. By condensation of *p*-nitroso-derivatives of tertiary amines with an amine in acid solution:



The instability of the simple indamines towards acids — they decompose into quinones and amines when acted upon by them — stands in the way of their practical use in dyeing. They are, however, important as intermediates in the preparation of the safranines.

All the simple indamines are blue or green; in addition to those already mentioned (Phenylene blue, Bindschedler's green), Toluylene blue:

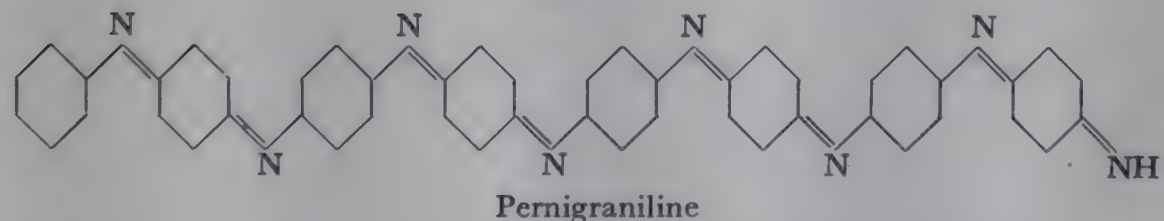
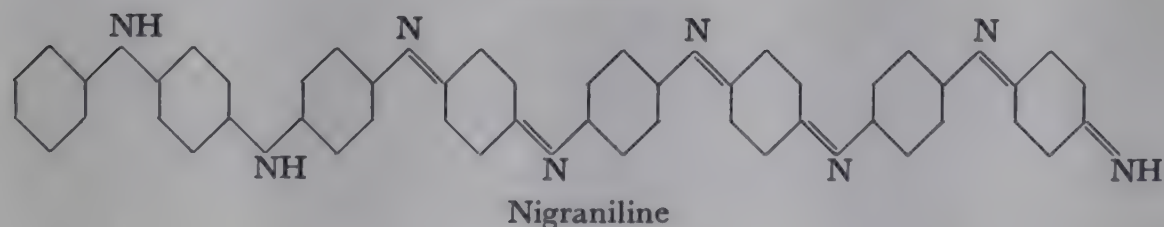
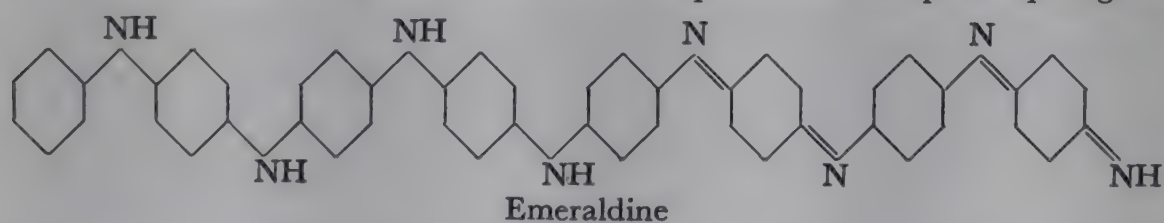


may be mentioned.

Very probably the indamines are involved also at certain oxidation stages in the preparation of the so-called Aniline black.

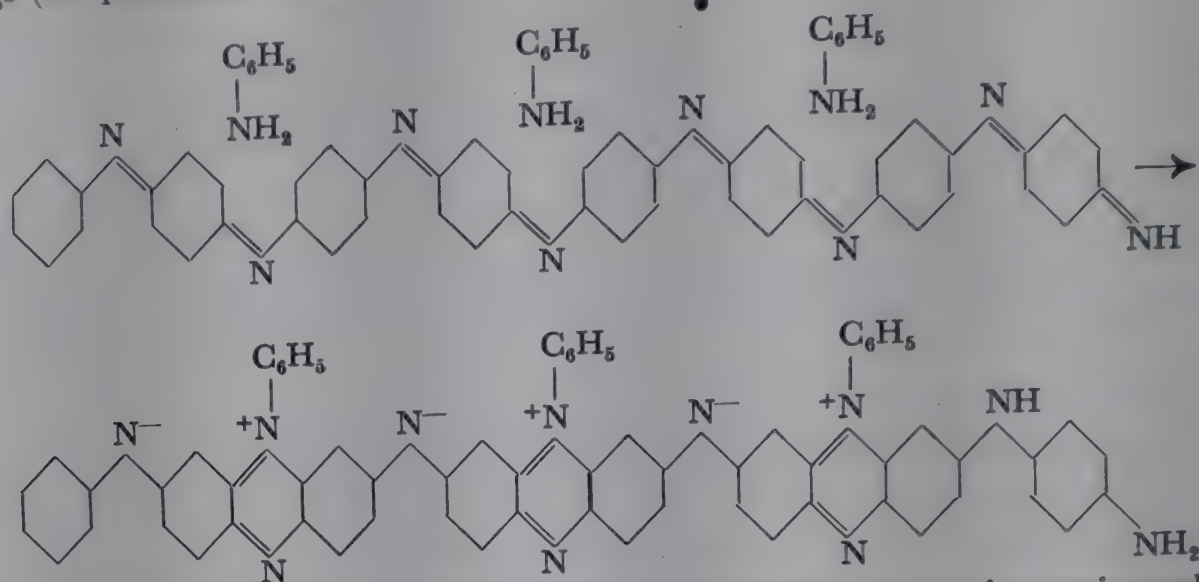
Aniline black. This exceedingly important dye is made by oxidizing aniline salts with potassium chlorate, dichromate, ferric compounds, etc., and is almost always produced directly on the fibre (cotton, and more rarely silk, and silk-cotton mixtures). Only small quantities are used as a mordant dye in calico printing. In order that the oxidation should pursue the desired course certain catalysts, oxygen carriers, are necessary, amongst which the most used are vanadium, copper, and iron salts.

According to the conditions of the oxidation, various stages of oxidation of Aniline black are reached. If the process is carried out in the cold, the so-called *emeraldine* can be isolated. It forms green salts, whilst as a base it is blue. According to Willstätter it is made by the condensation of eight aniline molecules, and has two quinonoid groupings. On further oxidation it is converted into the triquinonoid substance, *nigraniline*, and finally into the tetraquinonoid compound *pernigraniline*:



Emeraldine and nigraniline, and to a somewhat smaller degree also pernigraniline are very sensitive to acids, and fade. This behaviour agrees well with the assumed quinonimine structure. Industrially, however, a *non-fading* Aniline

black is produced by oxidizing at higher temperatures in the presence of aniline. Its almost complete stability towards acids and reducing agents is not compatible with a quinonimine formula. According to Green it is very probable that the non-fading Aniline black is formed from pernigraniline by condensation with three molecules of aniline, giving a phenylphenazonium salt with three phenazine rings (see phenazine dyes, p. 615):

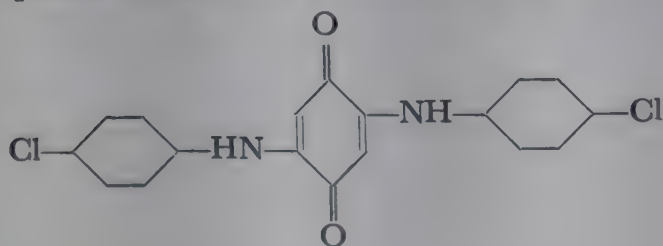


Non-fading Aniline black according to Green (Triphenyloctaphenazineazanium salt)

Aniline black is one of the fastest and most beautiful black dyes, and is therefore largely used, particularly for cotton dyeing. Runge first observed in 1834 the formation of a green dye when he acted upon a fabric treated with dichromate with aniline hydrochloride, but Lightfoot (1863) first developed the process to a technical method of dyeing with Aniline black, the aniline being oxidized in the presence of a copper salt.

DYES OF THE DIANILINO-BENZOQUINONE TYPE.

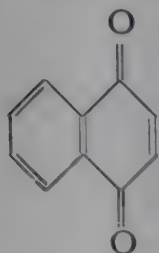
The action of aniline on *p*-quinone, giving rise to anilino- and dianilino-quinone, has been described on p. 577. Similarly constituted substances have recently found application as dyes. Thus, di-*[p*-chloranilino]-quinone, for example, which is prepared from quinone and *p*-chloroaniline, is a good dye for wool, and is used as a vat-dye. Its trade name is Helindon yellow CM.



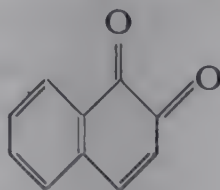
CHAPTER 46

NAPHTHAQUINONES. PHENANTHRENEQUINONE

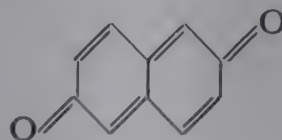
There are three quinones derived from naphthalene:



α -(*p*)-Naphthaquinone
1 : 4-Naphthaquinone



β -(*o*)-Naphthaquinone
1 : 2-Naphthaquinone



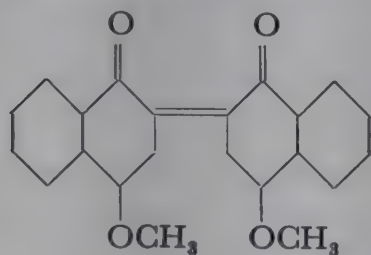
amphi-Naphthaquinone
2 : 6-Naphthaquinone

They are prepared by methods similar to those used in the benzoquinone series. α -NAPHTHAQUINONE is obtained from naphthalene, or more smoothly from 1 : 4-dihydroxy-, or 1-hydroxy-4-aminonaphthalene by oxidation with chromic acid. The compound shows similarities with *p*-benzoquinone. It is, like the latter, yellow, volatile in steam, and possesses a pungent smell. It melts at 125°.

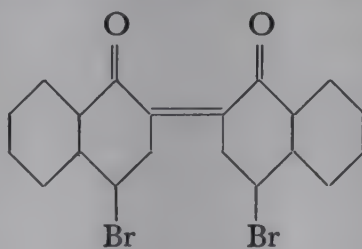
β -NAPHTHAQUINONE is prepared by oxidation of 1-amino-2-hydroxy-naphthalene. It crystallizes in red needles, which decompose between 115° and 120°. It is odourless, and is not volatile in steam. Its oxidizing power is less than that of the benzoquinones. It is scarcely attacked by sulphurous acid.

Whilst β -naphthaquinone itself has no chemical applications, its 4-sulphonic acid and β -naphthaquinone-4:6-disulphonic acid are used in the syntheses of dyes (indigoid dyes, Brilliant alizarin blue, etc.).

Recently, derivatives of binaphthylquinone have also been described, e.g.



and



amphi-NAPHTHAQUINONE is formed by oxidation of a 2:6-dihydroxynaphthalene suspension in benzene with lead dioxide. The compound crystallizes in yellow-red to brick-red prisms, is odourless, is not volatile, and can be preserved unchanged for a long time. On heating to 130–135° its colour becomes grey, and the product then dissolves in alkali.

amphi-Naphthaquinone shows the characteristic oxidizing power of the quinones, and indeed is a more powerful oxidizing agent than the α - and β -naphthaquinones.

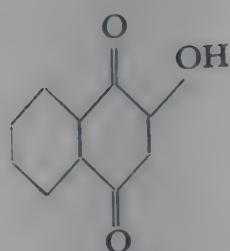
Dyes derived from the naphthaquinones.



Derivatives of α -naphthaquinone are occasionally met with in nature. *Juglone*, i.e. 5-hydroxy-1:4-naphthaquinone, is contained in the walnut shell and other green parts of the walnut tree, and is accompanied by *hydrojuglone* (1:4:5-trihydroxynaphthalene). *Juglone* is very widely spread in the *Juglandaceæ*, and forms yellow to brown-red prisms. It melts at 151–154°. A similar substance seems to occur in *Apocynaceæ*.

NAPHTHAQUINONES

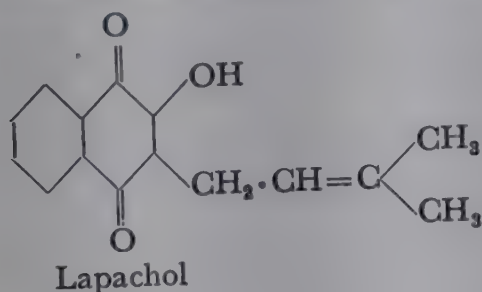
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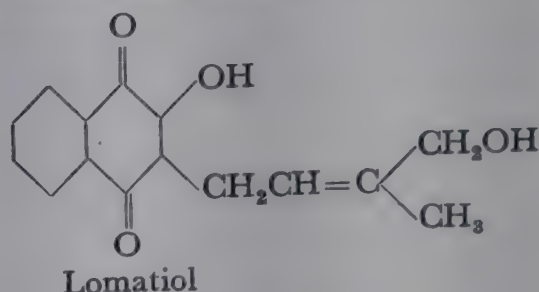
Lawsone

Structurally isomeric with juglone is *lawsone*, the dye of henna leaves. It has been proved both by degradation and synthesis to be identical with 2-hydroxy-1:4-naphthaquinone. Its methyl ether occurs in *Impatiens balsamina* L.

By the introduction of unsaturated side chains into this compound, *lapachol* (lapachoic acid), the colouring matter of lapacho wood and other tropical woods, and *lomatiol* (from the seeds of species of *Lomatia*) are obtained:



Lapachol

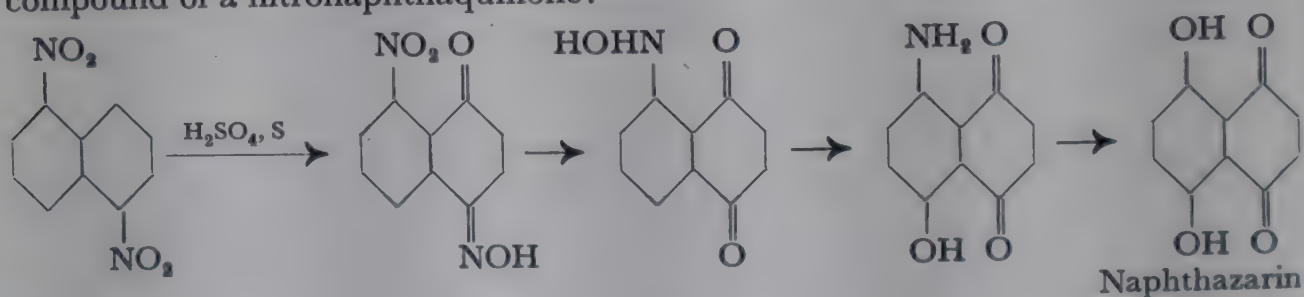


Lomatiol

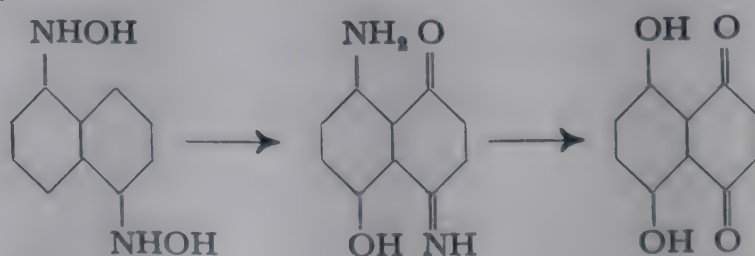
Both substances are yellow, and their alkali salts red. The melting point of lapachol is 140°.

The pigment *phthiocol* has been isolated from human tubercle bacilli. It is 2-methyl-3-hydroxy-1:4-naphthaquinone. However, it possibly does not occur as such in the tubercle bacillus but may be a fission product of vitamin K, being formed during the working up of the latter. It forms yellow prismatic needles, m.p. 173°.

NAPHTHAZARIN, known since about 1860 (Roussin), only came into practical use much later (1886, Bohn). The compound is obtained from 1:5-dinitronaphthalene on warming with fuming sulphuric acid and sulphur. The actual course of the reaction is not quite clear, but it presumably proceeds through an *isonitroso*-compound of a nitronaphthaquinone:



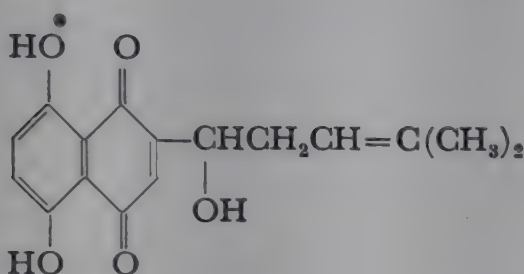
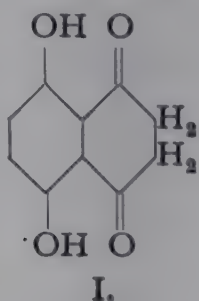
According to other views a dihydroxylamine-derivative of naphthalene is an intermediate product:



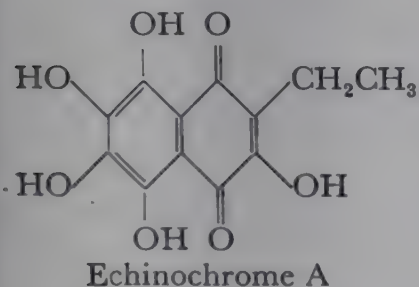
As the formula shows, naphthazarin is regarded as a dihydroxyderivative of α -naphthaquinone (Dimroth). With a chrome mordant it dyes a deep black,

extremely fast to acids, and it occurs in commerce as the soluble sodium sulphite compound, under the name Alizarin black S.

On reduction of naphthazarin with stannous chloride, a yellow *hydronaphthazarin* is produced, which has the constitution 1:4-diketo-5:8-dihydroxy-1:2:3:4-tetrahydronaphthalene (I). This is also formed from hydroquinone, succinic anhydride, and aluminium chloride. Zinc dust or sodium hydrosulphite converts naphthazarin into a very unstable, colourless, readily oxidizable dihydro-derivative, which has the formula (II):

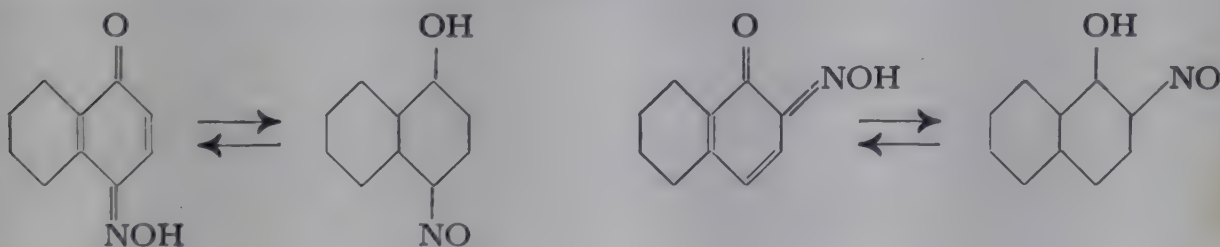


ALKANNIN, a dye from the root of *Alcanna tinctoria*, is a derivative of naphthazarin. It is given the formula shown at the side. (The quinonoid and benzenoid states of the two rings appear to be interchangeable). The compound is laevorotatory; m.p. 149°. The *d*-antipode, shikonin, occurs in shikon roots.



To the same group of compounds belongs ECHINOCHROME A, the prosthetic colouring matter of the sperm-activating and -agglutinating complex of the eggs of the sea-urchin *Arbacia postulosa*; it has also been produced synthetically.

NAPHTHOL GREEN. α - and β -Naphthaquinones react with hydroxylamine hydrochloride to give monoximes. The action of nitrous acid on the two naphthols gives the same products. Like the benzoquinone monoximes, the compounds derived from the naphthaquinones may, therefore, also be considered to exist in tautomeric forms, as oximes and nitroso-compounds:

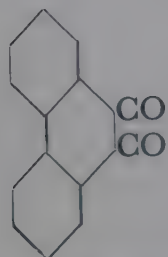
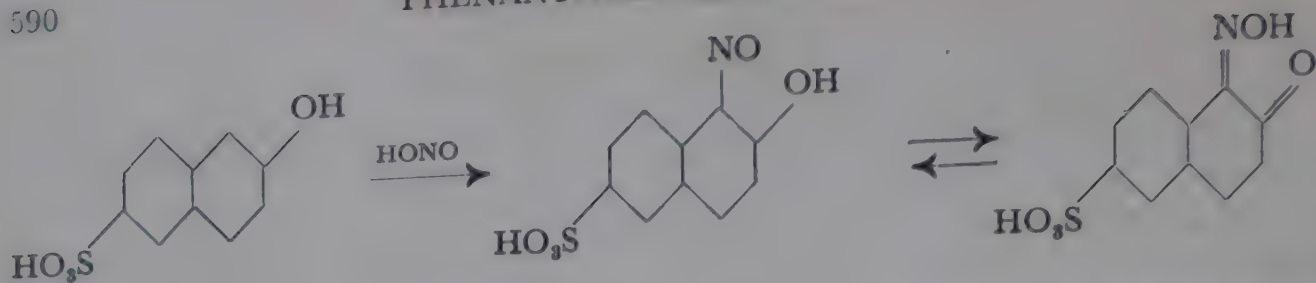


The compounds derived from ortho-(β -)naphthaquinone give dark green complex salts with iron compounds. They can therefore be used as mordant dyes on fabrics mordanted with iron.

For dyeing wool, the 6-sulphonic acid of nitroso- β -naphthol (iron lake = *Naphthol green*) is particularly used. It is obtained by the action of nitrous acid on Schäffer's acid:

PHENANTHRENEQUINONE

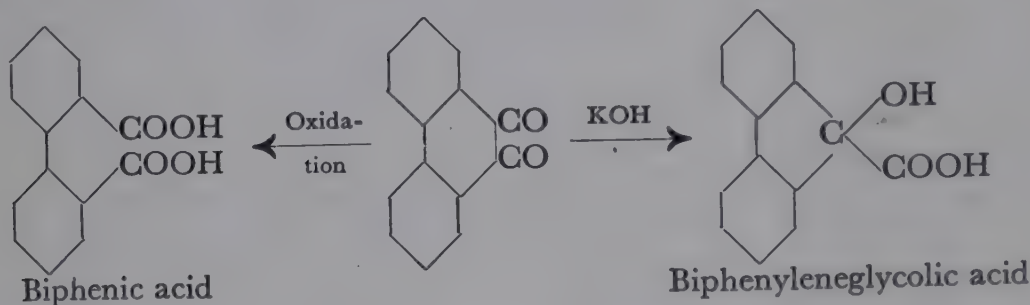
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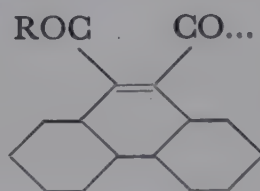
Phenanthrenequinone, the most important and the longest known of the quinones of the phenanthrene series, is very easily obtained by the oxidation of phenanthrene with chromic acid. It crystallizes in large, orange-coloured prisms, is odourless, and is not volatile. It melts at 209° .

Being an *o*-diketone it reacts with *o*-diamines to form phenazines (see p. 459). For the use of phenanthrenequinone as a reagent for thiotolene, see p. 393.

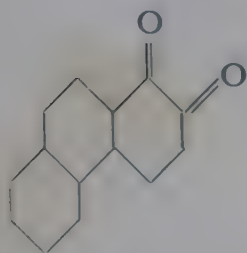
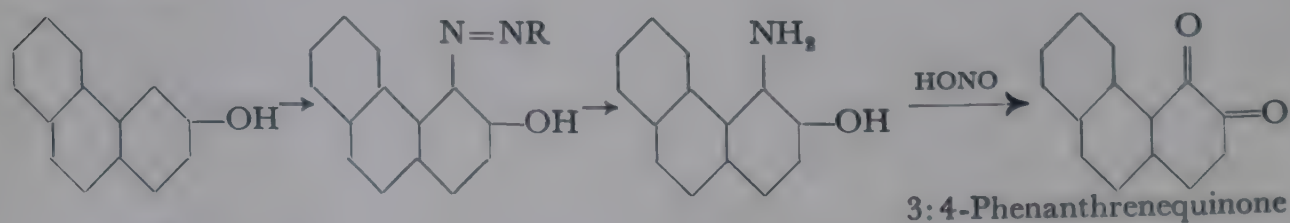
Oxidizing agents break down phenanthrenequinone into biphenic acid. When boiled with aqueous caustic potash it undergoes a "benzilic acid rearrangement", yielding biphenyleneglycolic acid, in a manner completely analogous to benzil (p. 515):



H. Goldschmidt prepared interesting unsaturated compounds of the so-called "free radical" type from phenanthrenequinone. They are given the following structure:



A second quinone derived from phenanthrene, 3:4-phenanthrenequinone has been prepared by L. F. Fieser. It is made from 3-hydroxyphenanthrene by coupling it with a diazonium salt, reducing the dye thus formed to the amine, and treating the latter with nitrous acid:



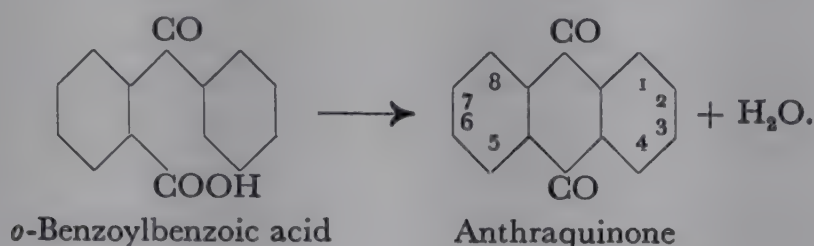
1:2-Phenanthrenequinone has also been prepared. It forms brilliant red needles melting at 222° .

CHAPTER 47

ANTHRAQUINONE AND ITS DERIVATIVES¹

Anthraquinone. This substance, which is exceedingly important in the dyeing industry, was prepared for the first time in 1840 by Laurent, who obtained it by treating anthracene with nitric acid. The oxidation of anthracene to anthraquinone proceeds so readily that the nitric acid does not act as a nitrating agent in this reaction.

In industry, dichromate and sulphuric acid are now used as the oxidizing agent. The formation of anthraquinone from *o*-benzoylbenzoic acid by heating with phosphorus pentoxide is valuable in connection with the determination of the constitution of the compound:

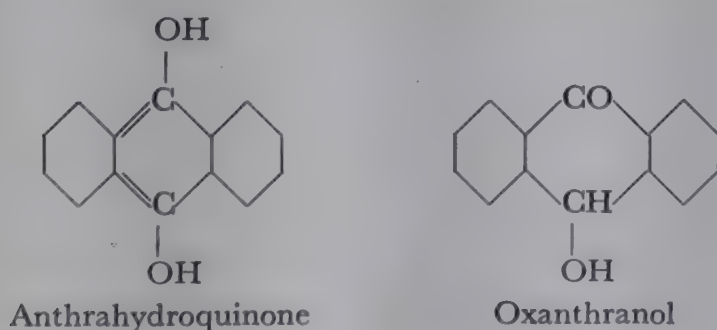


Anthraquinone forms yellow crystals, which melt at 284–285° (b.p. 382°). It is difficultly soluble in most solvents, is odourless, and not volatile in steam. Anthraquinone is attacked by reducing agents, but not very vigorously. In its entire behaviour it thus resembles a diketone rather than a quinone.

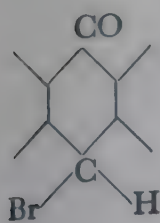
The first reduction product of anthraquinone, which is obtained by the action of zinc dust and alkali, is *anthrahydroquinone*, $\text{C}_6\text{H}_4 \begin{matrix} \text{C(OH)} \\ \text{C(OH)} \end{matrix} \text{C}_6\text{H}_4$. Its

brown crystals, melting at 180°, dissolve in alkalis with a deep red colour. The colour, however, disappears on shaking with air, as the substance is re-oxidized to anthraquinone. This reaction — turning red on treatment with zinc dust and alkali, and becoming colourless again on shaking with air — is a qualitative test for anthraquinone.

Anthrahydroquinone is tautomeric with *oxanthranol*:



¹ See E. DE BARRY-BARNETT, *Anthracene and Anthraquinone*, London, (1921). — H. E. FIERZ-DAVID, *Künstliche organische Farbstoffe*, Berlin, (1926), Ergänzungsband (1935). — J. HOUBEN, *Das Anthracen und die Anthrachinone mit den zugehörigen, vielkernigen Systemen*, Leipzig, (1929).



It has only recently been obtained by the hydrolysis of bromanthrone with water, as a colourless substance which does not fluoresce. The two tautomers can thus be isolated in the pure state. They are also stable in solution, but are easily converted one into the other by the action of catalysts (hydrogen chloride, sodium acetate). In alcoholic hydrogen chloride, for example, the equilibrium mixture contains 97 per cent anthrahydroquinone and 3 per cent oxanthranol.

Stronger reduction of anthraquinone (tin and hydrochloric acid) gives

anthrone, $\text{C}_6\text{H}_4 \begin{array}{c} \text{CO} \\ \diagup \quad \diagdown \\ \text{CH}_2 \end{array} \text{C}_6\text{H}_4$, which has already been mentioned in connection with its tautomeric form, anthranol.

Finally, anthraquinone may also be converted into anthracene by heating with hydriodic acid and phosphorus, or by distillation with zinc dust.

Anthraquinonesulphonic acids. The sulphonation of anthraquinone takes place fairly easily, mixtures of mono- and disulphonic acids usually being formed, the proportions of which vary with the conditions of sulphonation. The two position-isomeric monosulphonic acids of anthraquinone required by theory are known. One is designated the α -form, the other the β -form.

β -Anthraquinonesulphonic acid is the chief product (some of the α -form being produced at the same time) when anthraquinone is treated with concentrated sulphuric acid. Oddly enough, this state of affairs is completely reversed, and the α -sulphonic acid is almost the sole product, when mercury is present during the sulphonation. This phenomenon, discovered simultaneously by Dünschmann, Iljinski, and R. E. Schmidt, has been of great consequence for the development of the chemistry of anthraquinone, and also made many new disulphonic acids easily obtainable.

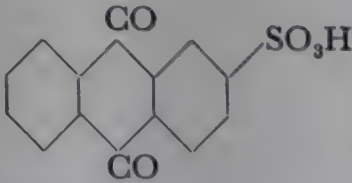
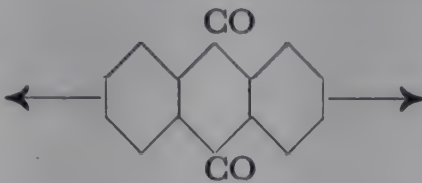
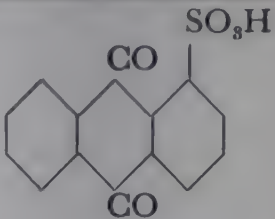
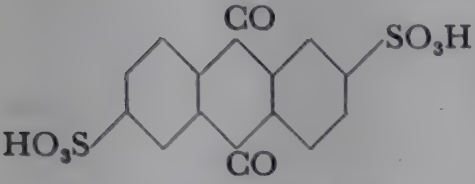
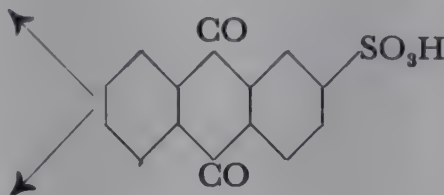
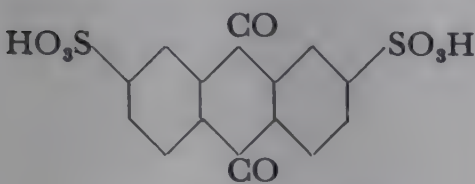
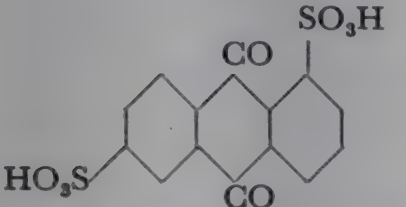
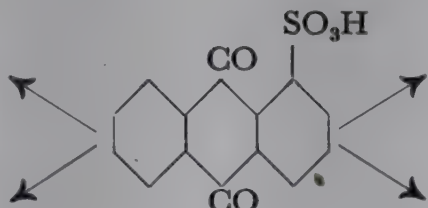
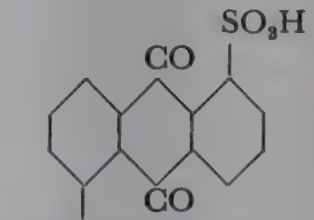
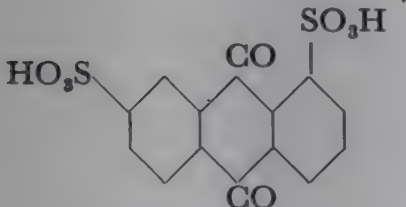
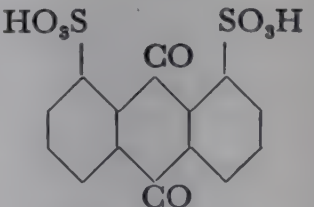
In the table (see page 593) the anthraquinone sulphonic acids obtained from anthraquinone and the two anthraquinonemonosulphonic acids by sulphonation with and without the addition of mercury are summarized.

Anthraquinone- α -sulphonic acid is also produced by a second, equally used technical process: heating the nitroanthraquinone concerned with aqueous sulphite solution under pressure.

Particularly, the sulphonic acid groups in the α -positions are very reactive. On heating such anthraquinonesulphonic acids with amines, aminoanthraquinones are produced, and when heated with lime, hydroxyanthraquinones. Treatment of the sulphonic acids with sodium chlorate and hydrochloric acid gives chloroanthraquinones, with elimination of the sulphonic acid radicals.

Hydroxyanthraquinones. Amongst the hydroxyanthraquinones by far the most important is ALIZARIN. It is found as the glycoside *ruberythric acid*, in the madder root (*Rubia tinctorum* and other species of *Rubia*). This gives on hydrolysis, alizarin and two molecules of sugar (glucose and D-xylose) which take part in the structure of the glycoside as the disaccharide primverose (= 6- $[\beta$ -D-xylosido]-D-glucose), attached at the hydroxyl in the β -position of the alizarin molecule.

The art of dyeing with madder seems to have been known to the ancient

Product of sulphonation without addition of mercury	Starting substance	Product of sulphonation with addition of mercury
 2-Sulphonic acid		 1-Sulphonic acid
 2 : 6-Disulphonic acid		
 2 : 7-Disulphonic acid		
 1 : 6-Disulphonic acid		 1 : 5-Disulphonic acid
 1 : 7-Disulphonic acid		 1 : 8-Disulphonic acid

Indians, Persians, and Egyptians. The plant was cultivated in Asia minor and Cyprus even thousands of years ago, and spread from there to Italy, and much later (from the XVIth century on) to France, Holland, and Alsace, where it was grown extensively. The elucidation of the constitution of the madder dye (initiated in 1860) by Graebe¹ and Liebermann, and its production by synthetic methods very soon drove the natural product completely from the market.

The artificial preparation of alizarin on a technical scale was the starting point for a series of brilliant syntheses which led to the replacement of important natural dyestuffs by synthetic products.

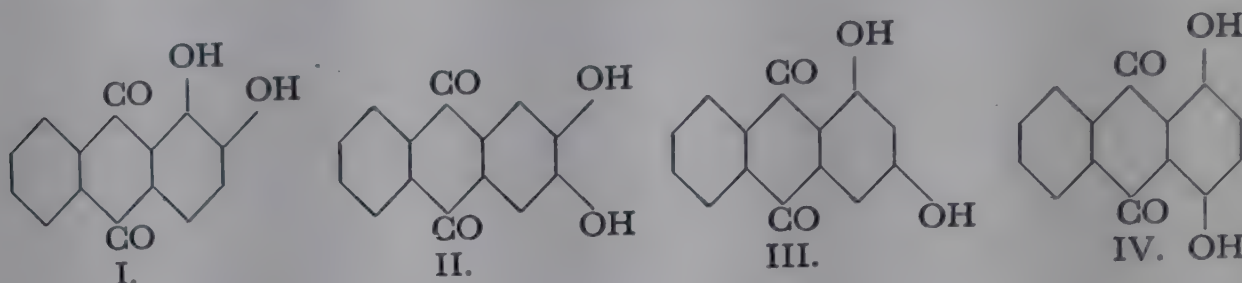
The proof of the constitution of alizarin is based on the following observations :

(a) Alizarin, $C_{14}H_8O_4$, gives anthracene on distillation with zinc dust. It can

¹ See GRAEBE's *Untersuchungen über Chinone*. Ed. by H. Dekker, Leipzig, (1911).

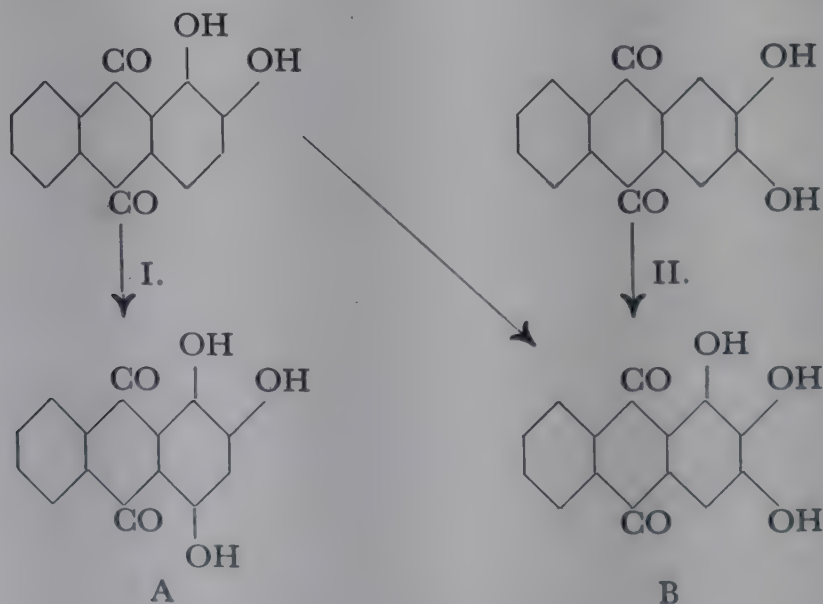
be obtained from a dibromoanthraquinone by fusion with alkali. Thus only the formula of a dihydroxyanthraquinone comes into consideration.

(b) By oxidation alizarin is broken down to phthalic acid. It therefore contains one hydroxyl-free benzene nucleus. The positions of its two OH groups are thus limited to the following four possibilities:

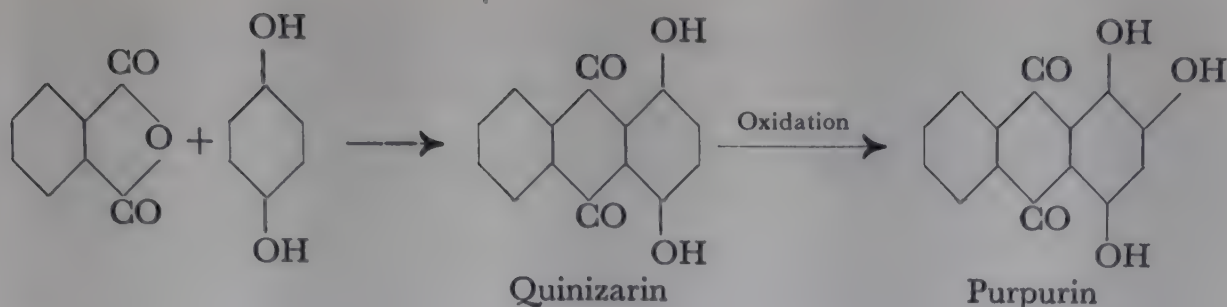


(c) On heating phthalic anhydride with pyrocatechol and sulphuric acid two dyes are obtained: alizarin and hystazarin. Both must have the hydroxyl groups ortho to each other. The one corresponds to formula I above, the other to formula II. The correct allocation of the two formulæ to the isomeric dyes can be made by a slightly indirect method.

(d) Alizarin is oxidized by manganese dioxide to a trihydroxyanthraquinone, *purpurin*. This anthraquinone dye also contains a hydroxyl-free benzene nucleus, since, on degradation, it gives phthalic acid. The oxidation of the dihydroxyanthraquinone (I) can give two different trihydroxyanthraquinones, (A) and (B), which both contain the hydroxyl groups in the same nucleus. The dihydroxyanthraquinone (II), however, can only give (B):



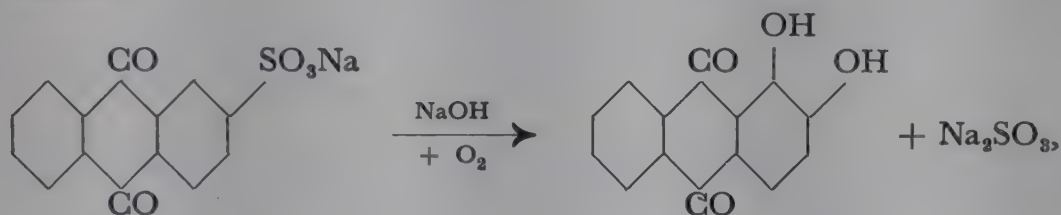
If, therefore, it can be proved that purpurin has formula (A), then alizarin, its parent substance, must have the dihydroxyanthraquinone structure (I). This is, in fact, easily done; for purpurin can also be formed by the condensation of phthalic anhydride with hydroquinone and subsequent oxidation of the dihydroxyanthraquinone (quinizarin):



This method of formation determines the positions of the hydroxyl groups in purpurin unequivocally, and therefore, according to what has been said above, those in alizarin. Alizarin therefore has the constitution (I).

Alizarin crystallizes in red prisms, which melt at 289° . It is difficultly soluble in water, but is readily soluble in alkalis and in alcohol.

The technical synthesis of alizarin — fusion of anthraquinonesulphonic acid with sodium hydroxide — was discovered almost simultaneously by Graebe and Liebermann, W. H. Perkin, and also Rieser in the I. G. works, Höchst. Whilst at first the alkali fusion was carried out without the addition of any further oxidizing agent, the introduction of the second hydroxyl group being effected by the atmospheric oxygen:

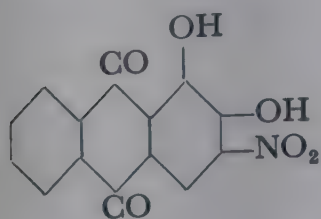


it was soon found that the process could be improved, and would go nearer to completion if an oxidizing agent were added to the melt. Usually potassium chlorate or potassium nitrate is used. The first synthetic alizarin came on to the market in 1871.

Alizarin is a typical mordant dye, and its application to the fibre requires a special pre-treatment of the fabric. In spite of these difficulties, alizarin (madder) was used in the East in ancient times. In France and England the art of dyeing with madder was introduced only in the XVIIIth century. Alizarin is usually used with an aluminium mordant and a deep, brilliant red is obtained. Previous to this, however, the cotton is impregnated with an oil. In the earlier process (the so-called ancient red process) this was done with a rancid olive oil (Tournant oil) in which potassium carbonate solution was emulsified. The more recent, and now solely used "new red process" uses in its place the so-called *Turkey-red oil*, which is made by treating castor oil with concentrated sulphuric acid, and then neutralizing the liquid. The cotton is steeped in this, dried, and then placed in a bath of aluminium sulphate or acetate. The alumina now combines with the sulphonated oleic acids to give salts. In order to make these completely insoluble, the fabric is then drawn through a chalk suspension in a bath. It is now ready to be dyed with alizarin, to which some tannin is added.

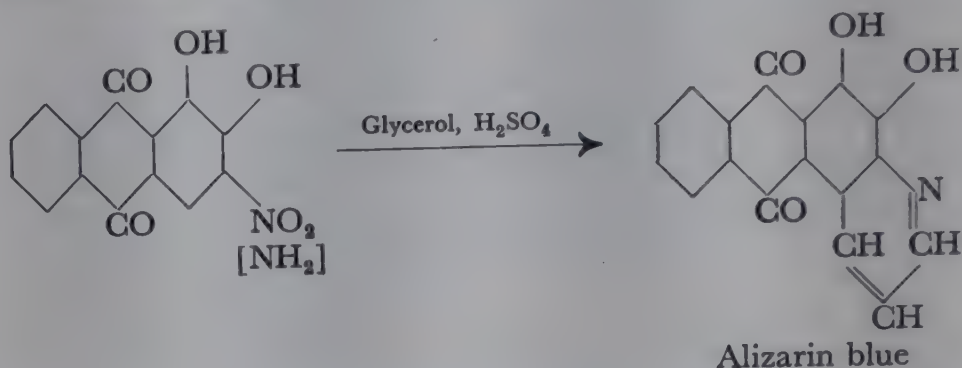
Although alizarin is most often used with an aluminium mordant, it is also often employed in the form of iron and chrome lakes. With an iron mordant various violet colours, and with a chromium mordant brown-red shades are obtained. In wool and silk dyeing alizarin is likewise used with a metallic mordant.

Alizarin red, despite its being the most beautiful and fastest red for cotton, is only occasionally used to-day owing to the complicated method of dyeing necessary. It has been replaced by various naphthol AS dyes (p. 495). Such has also been the case with other mordant dyes of the polyhydroxyanthraquinone series.



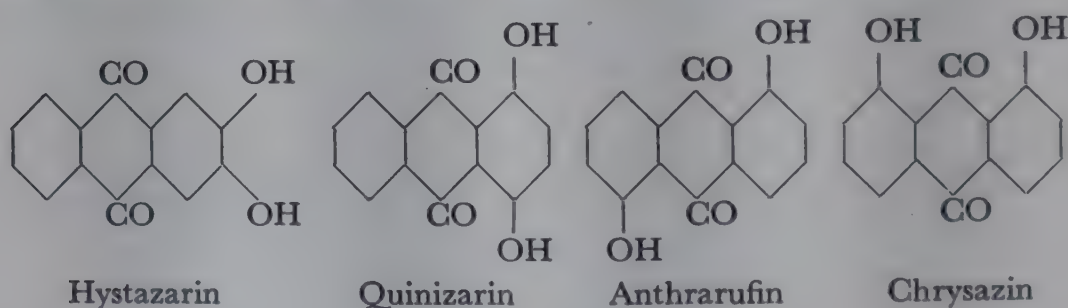
ALIZARIN ORANGE. This dye is formed from alizarin by nitration with nitric acid. Its colour with an alumina mordant is orange, and on a chromium mordant red-brown.

If Alizarin orange (or a mixture of Alizarin orange and aminoalizarin) is warmed with glycerol and concentrated sulphuric acid, a pyridine ring is formed, as in Skraup's synthesis of quinoline (see Ch. 61):



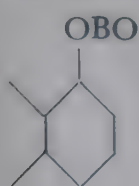
The new substance, *Alizarin blue*, is one of the most important mordant dyes. Its indigo-blue colours on chrome-mordanted cotton have excellent fastness.

Amongst other dihydroxyanthraquinones must be mentioned *hystazarin*, *quinizarin*, *anthrarufin*, and *chrysazin*:



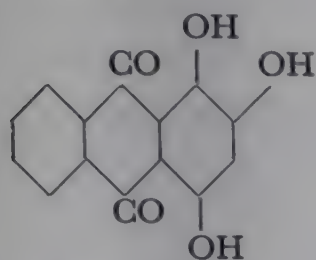
They all have small powers of attachment to mordants, and are worthless as dyes. On the other hand they are used as the starting points in the preparation of acid wool dyes, etc.

The synthesis of hystazarin from phthalic anhydride and pyrocatechol has already been referred to. A monomethyl ether of the compound has been detected in chay root. Quinizarin is formed by fusing together phthalic anhydride and hydroquinone with sulphuric acid. Technically it is made by the oxidation of anthraquinone with fuming sulphuric acid in the presence of boric acid. This important oxidation process, which goes under the name of the Bohn-Schmidt reaction, enables hydroxyl groups to be introduced into anthraquinone and hydroxyanthraquinone derivatives, and has become the source of numerous new dyes. The boric acid forms esters with the hydroxyanthraquinones, thus protecting them from further oxidation, and therefore exerts a moderating influence on the course of the reactions.

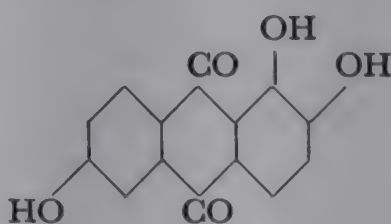


Anthrarufin and chrysazin are obtained from the corresponding disulphonic acids by heating with lime and water.

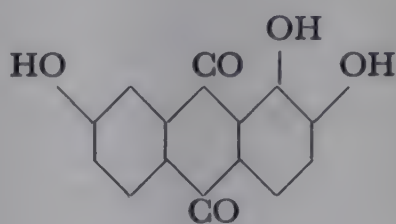
Trihydroxyanthraquinones. To this class belong *purpurin*, *flavopurpurin*, and *anthrapurpurin*:



Purpurin



Flavopurpurin



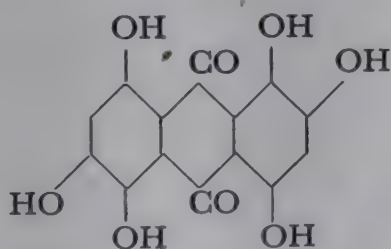
Anthrapurpurin

Purpurin is found together with alizarin in the madder root. It is prepared synthetically from alizarin by oxidation with manganese dioxide and sulphuric acid, but only plays a small part as a dye (used in calico printing; its chrome lake is a red-violet). Flavopurpurin and anthrapurpurin are formed in the same way as alizarin by the fusion of sulphonic acids with alkali and chlorate, the first being obtained from 2:6-, and the second from 2:7-anthraquinonesulphonic acid. They have some use in calico printing and give with an aluminium mordant a scarlet, and a yellow-red colour, respectively.

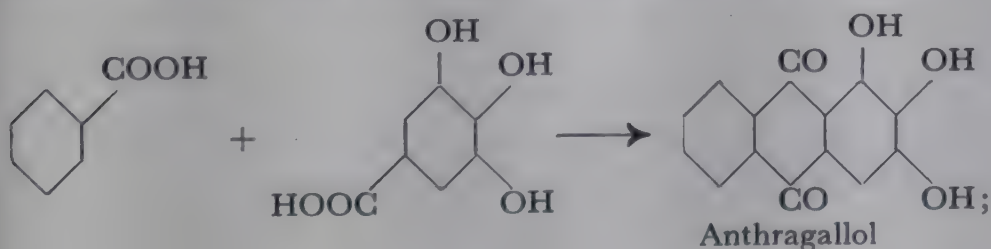
Polyhydroxyanthraquinones. ALIZARIN BORDEAUX, 1:2:5:8-tetrahydroxyanthraquinone, is obtained from alizarin by heating with fuming sulphuric acid and boric acid (Bohn-Schmidt reaction). It is a cotton dye. Its chrome lake is brownish violet, and with an aluminium mordant it gives a bordeaux colour.

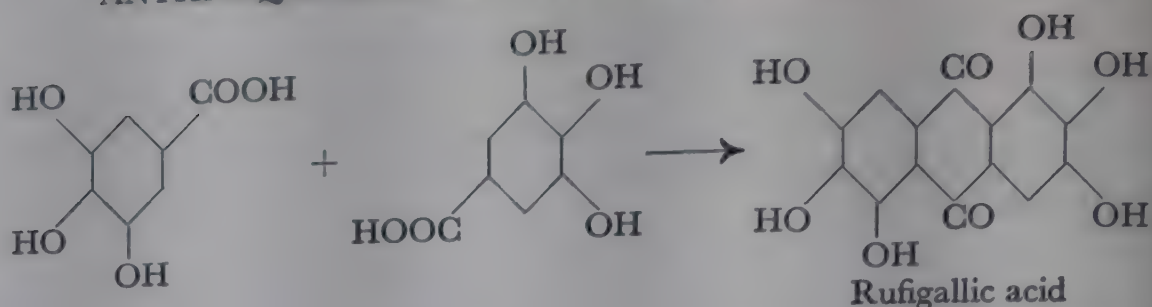
ALIZARIN CYANIN R, 1:2:4:5:8-pentahydroxyanthraquinone. Gives a reddish blue shade with a chromium mordant.

ANTHRACENE BLUE WR. is formed by heating 1:5-dinitroanthraquinone with fuming sulphuric acid. It gives a reddish blue colour on chrome-mordanted wool, but is scarcely used nowadays. Its formula is:



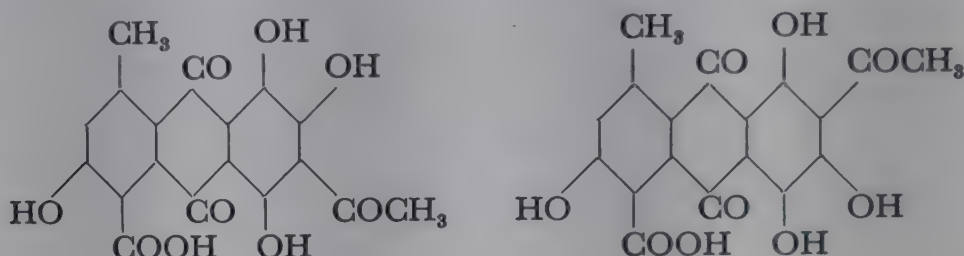
RUFIGALLIC ACID. The heating of equivalent parts of benzoic acid and gallic acid with concentrated sulphuric acid leads to two dyes: anthragallol and rufigallic acid. They owe their formation to the following processes:





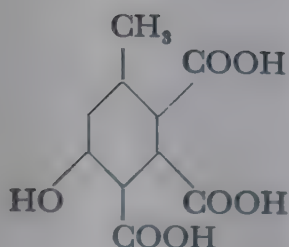
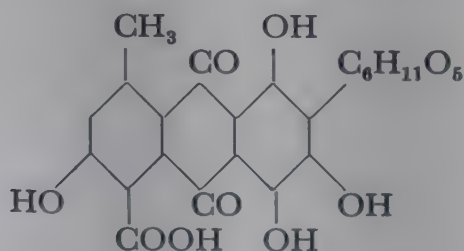
The mixture of the two compounds, in which anthragallol predominates, comes on to the market as Anthracene brown FF, or Alizarin brown. The aluminium and chromium lakes, usually produced on cotton, are reddish brown.

KERMES (KERMISIC ACID). This dye, now no longer used, consisted of certain kinds of dried, female, cochineal insects (especially *Coccus ilicis*). It was superseded, even as far back as the XVIth century, by cochineal. Its colouring principle is kermisic acid, a hydroxyanthraquinone derivative, for which the following two formulæ come into consideration:



COCHINEAL (CARMINIC ACID). The female of the cochineal insect (*Coccus cacti*) which breeds on cactus plantations in Central America, particularly Mexico, is killed shortly before laying its eggs, by steam or heating. When dried and ground it forms the so-called cochineal, one of the fastest, most beautiful, but most expensive mordant dyes. It is used chiefly for dyeing silk or wool. Specially brilliant is its tin lake, known as Cochineal scarlet.

The colouring matter of cochineal is carminic acid. Its constitution is not yet fully clear. It is a complicated hydroxyanthraquinone derivative, to which Dimroth assigns the structure:

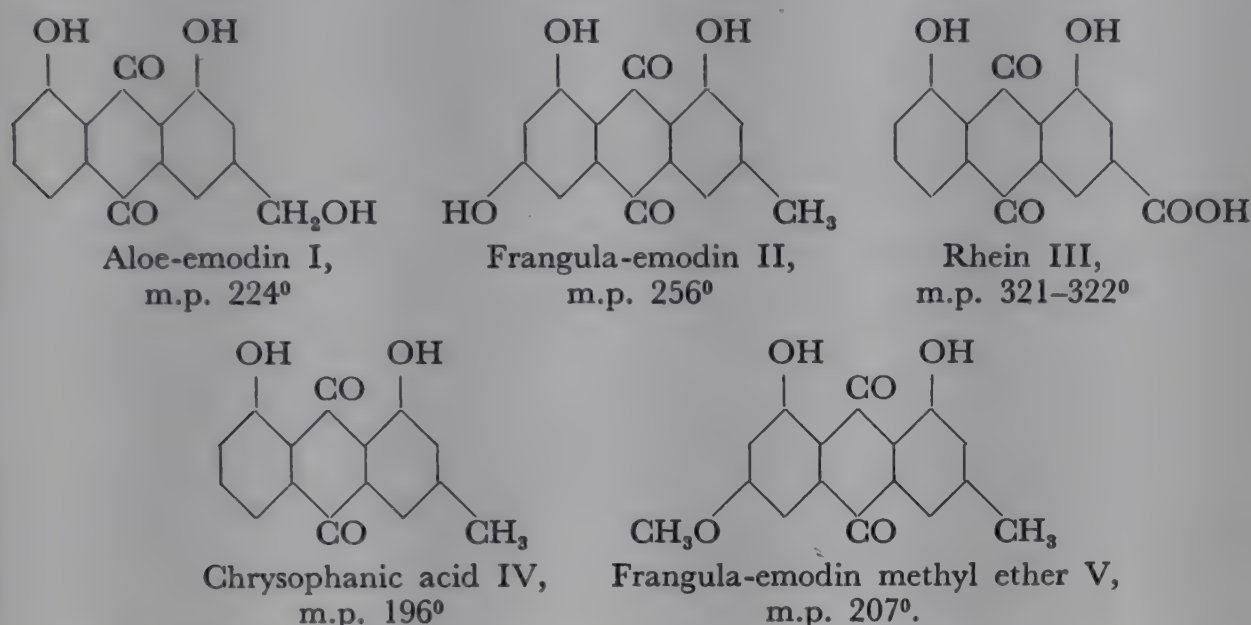


On oxidation it breaks down to cochenillic acid (formula on the left), which is also encountered as a degradation product of kermisic acid.

In the fungi of the species *Boletus*, which includes the edible mushroom, is the dye *boletol*, which is a 1:2:4-trihydroxyanthraquinone-5- (or 8-)carboxylic acid (Kögl). The yellow compound present in the fungus is converted into a blue pigment on cutting the fungus. The latter may be a diquinone produced by the action of oxygen and an oxidase (Bertrand).

EMODINS. In many laxative drugs there are some isomeric trihydroxyanthraquinone derivatives which occur, in the plants from which the drugs are obtained, partly free, partly in the form of glycosides or as methyl ethers, and partly as reduction products. They are the active principles of the plants. They are given the collective name of emodin.

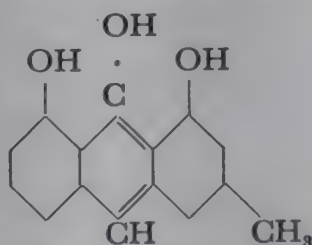
Aloe-emodin (I), 3-(hydroxymethyl)-1:8-dihydroxyanthraquinone, is contained in aloes; *frangula-emodin* (II) is contained in Chinese rhubarb, and in varieties of *Rumex*, *Polygonum*, and *Rhamnus*. *Rhein* (III) is found in rhubarb, besides the important *chrysophanic acid* (IV), which is usually accompanied by *frangula-emodin methyl ether* (V):



The formulæ show clearly the close interrelationship of all these derivatives of anthraquinone. Their constitution has been ascertained partly by degradation and partly by synthesis (Léger, Oesterle, Eder).

Hydroxyanthraquinones are also widespread in micro-organisms. The anthraquinone derivative *helminthosporin* is a product of the metabolism of *Helminthosporium gramineum*. It is 1:5:8-trihydroxy-3-methylantraquinone. 1:4:5:8-Tetrahydroxy-3-methylantraquinone is found in other varieties of *Helminthosporium*. *Aspergillus glaucus* contains among other compounds *physcion*, 4:5-dihydroxy-7-methoxy-2-methylantraquinone (Raistrick).

CHRYSAROBIN finds wide application in medicine for the treatment of skin affections (eczema, psoriasis, etc.). It is a methyl-dihydroxy-anthranol (m.p. 203-204°):

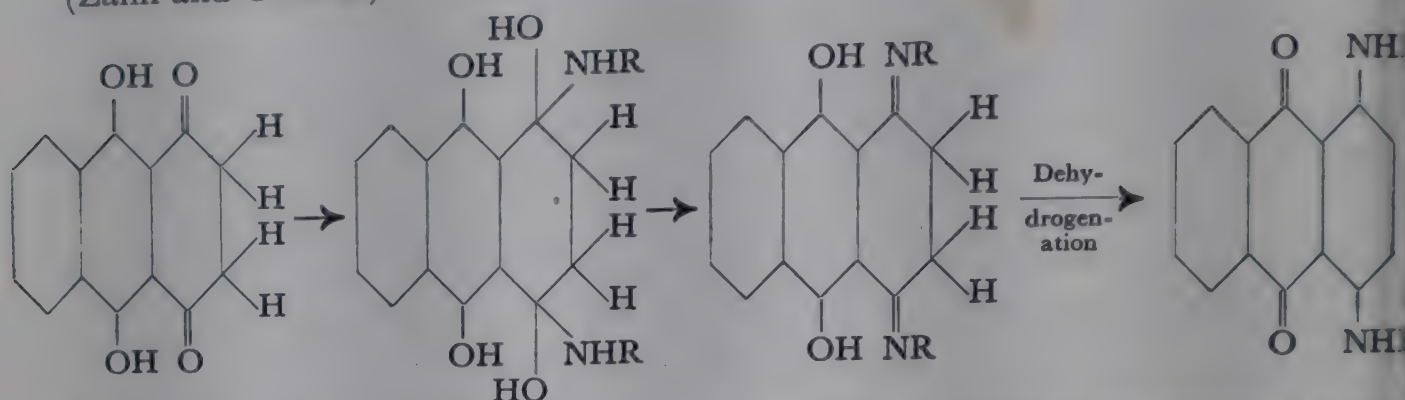


It is formed by partial reduction of chrysophanic acid, and is reconverted into the latter by atmospheric oxygen. The compound is a constituent of goa powder (araroba), which is formed in the pith-cavities of certain Brazilian trees.

Aminoanthraquinones (acid wool dyes of the anthraquinone series).

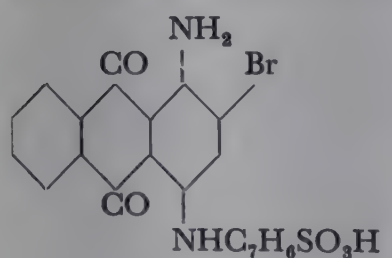
The hydroxyl groups of hydroxyanthraquinones and particularly of their hydro-derivatives, can be replaced by amino-radicals on heating with amines,

boric acid being here an excellent condensing agent. Hydroxyl groups in the α -positions react particularly readily. These reactions were discovered by R. E. Schmidt, and have led to the opening up of a large and important group of new dyes. In the case of the hydro-derivatives of the hydroxyanthraquinones the reactions probably occur with these substances in the keto form (quinone form) (Zahn and Ochwat):

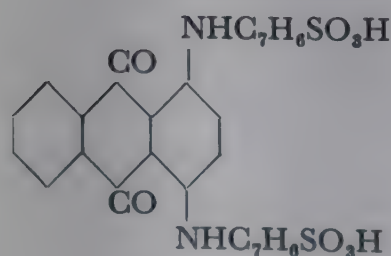


Such aminoanthraquinones are used in the dyeing industry in the form of their sulphonic acids. These are readily obtained from the amines by the ordinary process of sulphonation, the sulphonic acid radical entering the arylamino group. Analogous substances are formed by heating α -nitro- and α -chloroanthraquinone with amines, the NO_2 and Cl groups respectively being replaced.

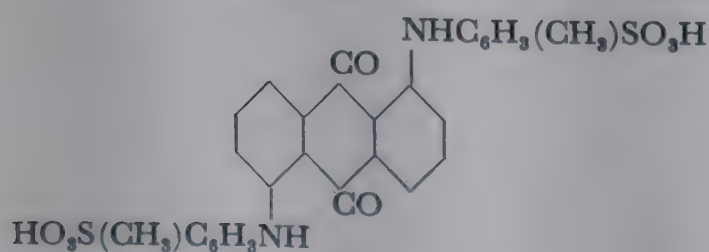
The sulphonated aminoanthraquinones are acid dyes for wool, which are highly prized on account of their fastness, and the brilliance of their colours. Only a few representatives from this large group can be dealt with here:



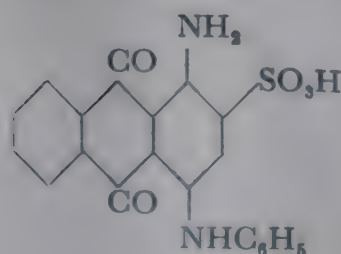
ALIZARIN PURE BLUE B (made from 1-amino-4-hydroxyanthraquinone and *p*-toluidine, with subsequent sulphonation and bromination).



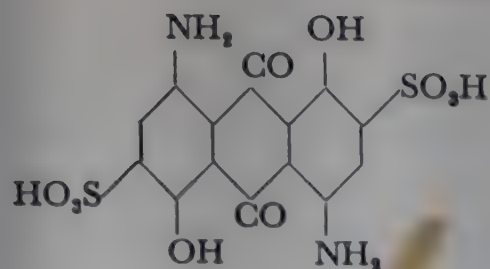
ALIZARIN CYANIN GREEN G (made from quinizarin and *p*-toluidine).



ANTHRAQUINONE VIOLET (made from 1:5-dinitroanthraquinone and *p*-toluidine).



ALIZARIN SAPHIROLE A, possesses a sulphonamic acid group in the anthraquinone nucleus. It is a pure blue and is fast to washing and acids.



ALIZARIN SAPHIROLE B, the oldest member of this class.

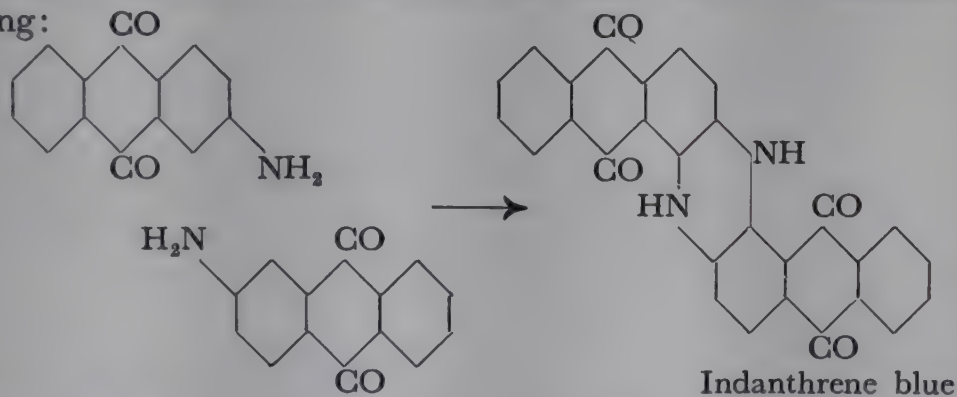
Vat-dyes of the anthraquinone series¹

Tyrian purple, and indigo were for a long time the only vat-dyes. A new era opened for this class of dyes when in 1901 René Bohn made the surprising observation that β -aminoanthraquinone produced, when fused with alkali, an exceedingly fast, blue vat-dye, indanthrene. Later, it was found that many other derivatives of anthraquinone were also suitable for the synthesis of vat-dyes, and to-day this class of compounds is not only one of the most comprehensive and best developed, but also one of the most important technically, since there are many very fast dyes in the series. The strongly alkalinity of the vat in the case of anthraquinone dyes excludes their use for dyeing wool. On the other hand they are extremely valuable for dyeing cotton.

It is convenient to distinguish various sub-groups:

(a) Indanthrene dyes.

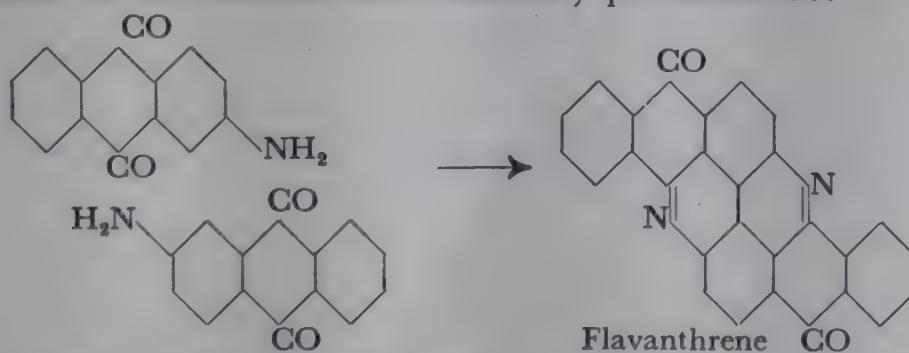
INDANTHRENE BLUE, the first dye of this series to become known, is formed by fusing β -aminoanthraquinone with caustic potash at about 250°. It contains a hydrophenazine ring:



It is exceedingly fast to light, but less so to chlorine.

(b) Flavanthrene dyes.

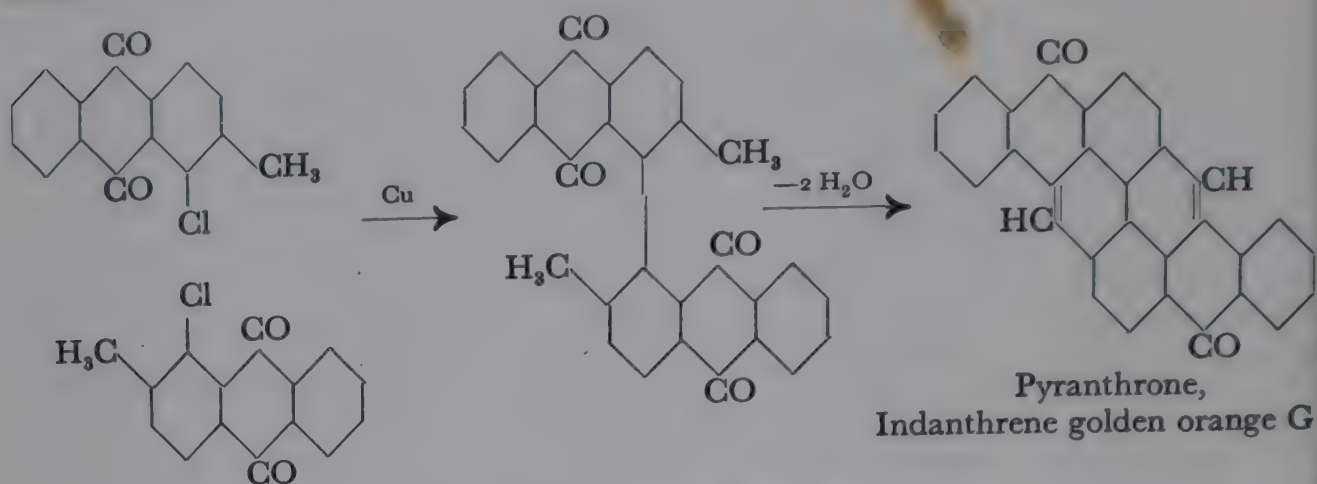
INDANTHRENE YELLOW G or FLAVANTHRENE is formed in addition to indanthrene blue on fusing β -aminoanthraquinone with alkali, especially if the temperature is raised. It is more conveniently prepared by acting on β -aminoanthraquinone in nitrobenzene with antimony pentachloride:



Flavanthrene dyes yellow. Its vat is blue.

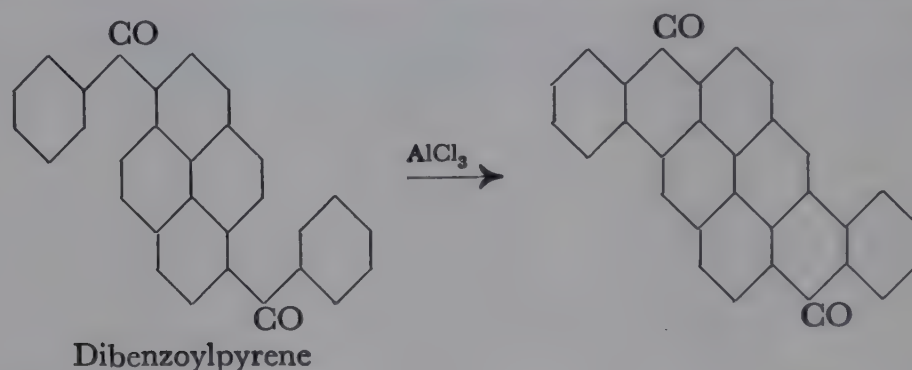
¹ See H. TRUTWIN, *Enzyklopädie der Küpenfarbstoffe*, Berlin, (1920).

INDANTHRENE GOLDEN ORANGE G or PYRANTHRONE (R. Scholl). 1-Chloro-2-methyl-anthraquinone gives 2:2'-dimethyl-1:1'-dianthraquinonyl on heating with copper powder. If this is warmed with zinc chloride or solid caustic potash, two molecules of water are eliminated and ring closure occurs, pyranthrone being formed:



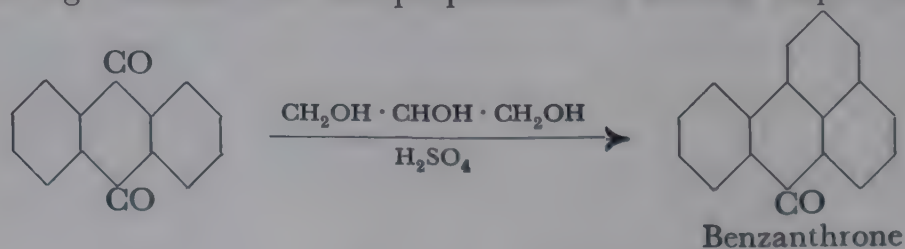
Pyranthrone dyes a very fast orange from a fuchsin-red vat.

The constitution of this dye is arrived at from another method of formation, namely, by heating dibenzoylpyrene strongly with aluminium chloride:

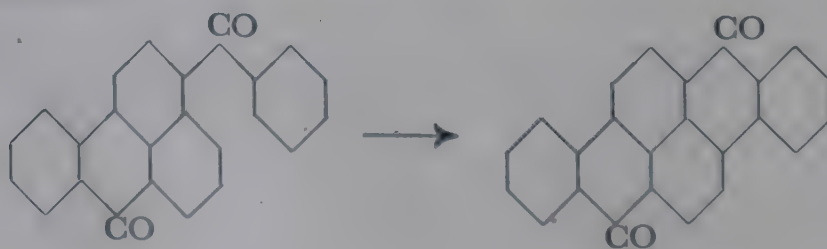


(c) Benzanthrone dyes.

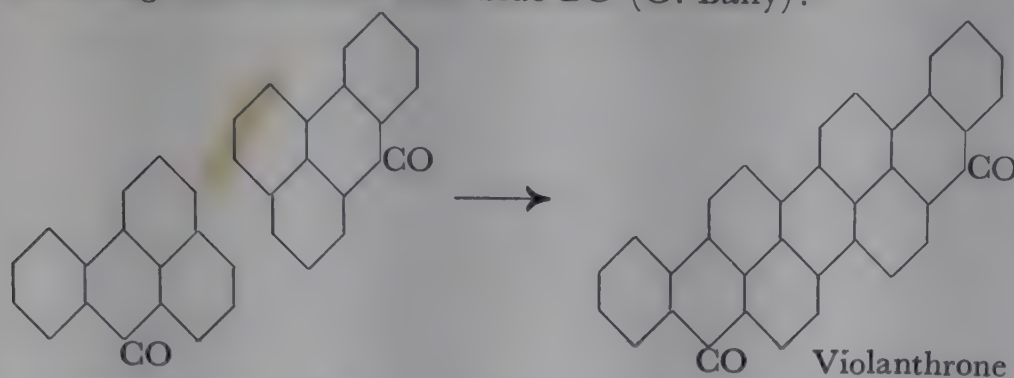
When anthranol or anthraquinone is heated with glycerol and sulphuric acid, it is converted, with the closure of a new benzene ring, into *benzanthrone*. It is the starting substance for the preparation of several important vat-dyes:



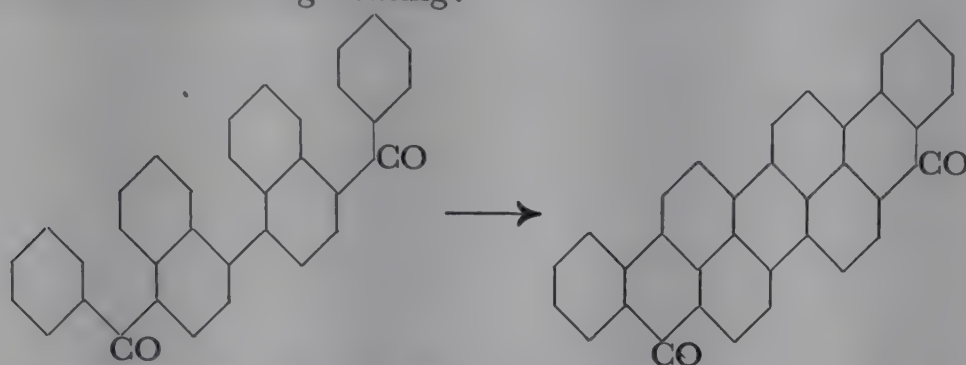
INDANTHRENE GOLDEN YELLOW GK. is a chloro-derivative of *dibenzpyrene-quinone*, which may be obtained from benzoylbenzanthrone by strong heating with aluminium chloride:



VIOLANTHRONE or **INDANTHRENE DARK BLUE BO**. If benzanthrone is subjected to fusion with caustic potash, two molecules condense with the elimination of hydrogen, forming Indanthrene dark blue BO (O. Bally):

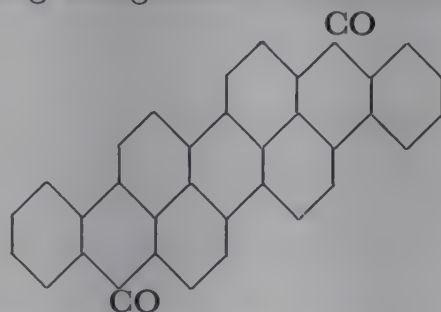


This substance dyes a deep violet-blue from a violet vat, and the colour is extremely fast to washing, light, and chlorine. Its constitution is arrived at since it is also the product of the reaction between dibenzoyl- $\alpha:\alpha'$ -binaphthyl and aluminium chloride on strong heating:



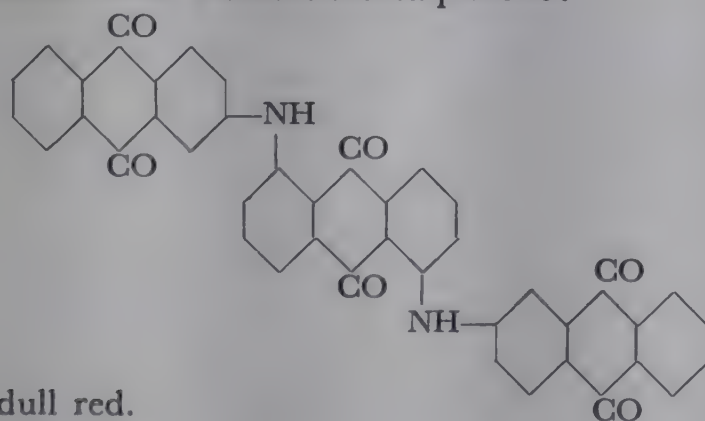
The beautiful *Caledon jade green B* or *Indanthrene brilliant green B*, distinguished by its excellent fastness, is a dimethoxy-derivative.

ISOVIOLANTHRONE, or **INDANTHRENE VIOLET R EXTRA**, isomeric with violanthrone, is formed by heating halogenated benzanthrone with caustic potash to 130–150° (Bally):



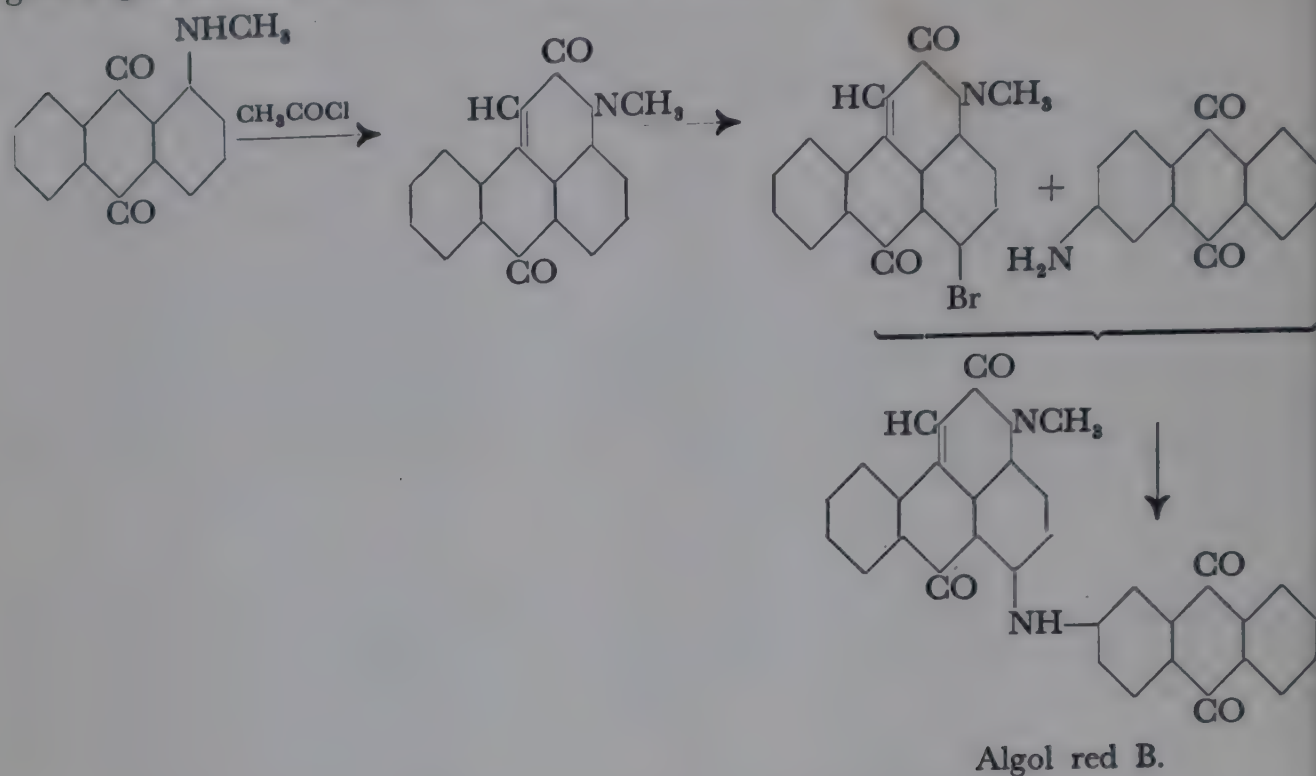
(d) Anthraquinonimine dyes and acylaminoanthraquinones.

INDANTHRENE BORDEAUX B (Isler) is formed by condensation of 1:5-diaminoanthraquinone with 2-chloroanthraquinone:

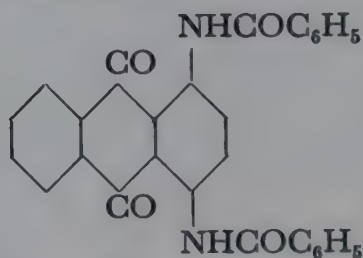


It dyes cotton a dull red.

ALGOL RED B. 1-Methylamino-anthraquinone is acetylated, and condensed with loss of water to N-methylantraquinonepyridone, which is then brominated in the 4-position. This bromo-compound reacts with β -aminoanthraquinone to give Algol red B, which dyes pink from a yellow-red vat:

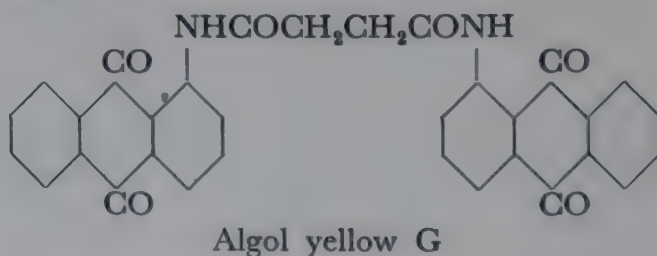


ALGOL RED 5 G is dibenzoyl-1:4-diaminoanthraquinone.



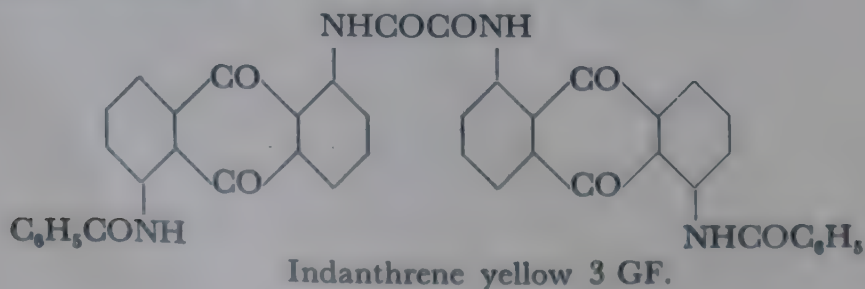
It dyes cotton a very fast scarlet from a violet vat.

ALGOL YELLOW G. This compound is prepared by heating α -aminoanthraquinone with succinic acid in nitrobenzene:



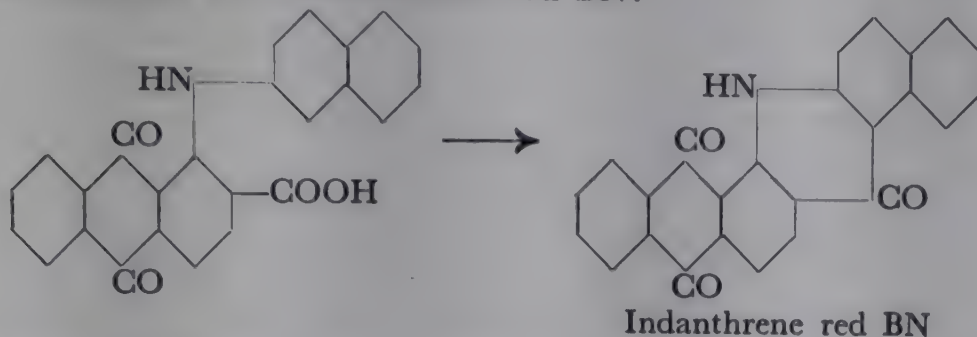
Algol yellow G dyes cotton one of the fastest yellows.

INDANTHRENE YELLOW 3 GF. is a very fast, yellow dye:



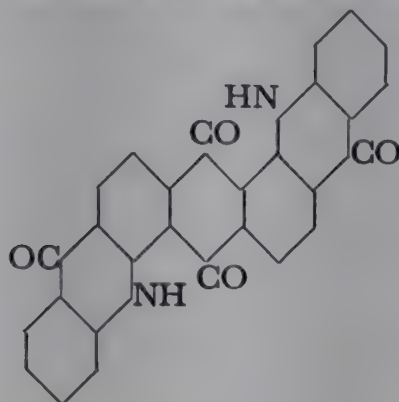
(e) Anthraquinoneacridone dyes.

INDANTHRENE RED BN. 1-Chloroanthraquinone-2-carboxylic acid can be condensed with β -naphthylamine and copper powder to 1-(2-naphthylamino)-anthraquinone-2-carboxylic acid, which, on treatment with phosphorus pentachloride is converted into Indanthrene red BN:

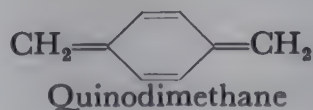
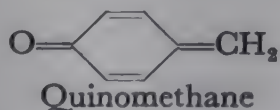


It dyes a pure red from a claret-coloured vat.

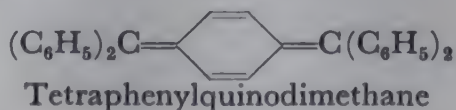
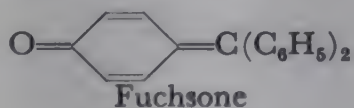
Another anthraquinoneacridone dye is INDANTHRENE VIOLET RN (Ullmann):

**CHAPTER 48****DYES DERIVED FROM FUCHSONE**

If the oxygen atoms of *p*-benzoquinone are imagined to be replaced successively by methylene groups, the formulæ of two compounds are obtained which may be regarded as derivatives of methane and quinone, and may be called *quinomethane*, and *quinodimethane* according as one or two oxygen atoms are replaced:

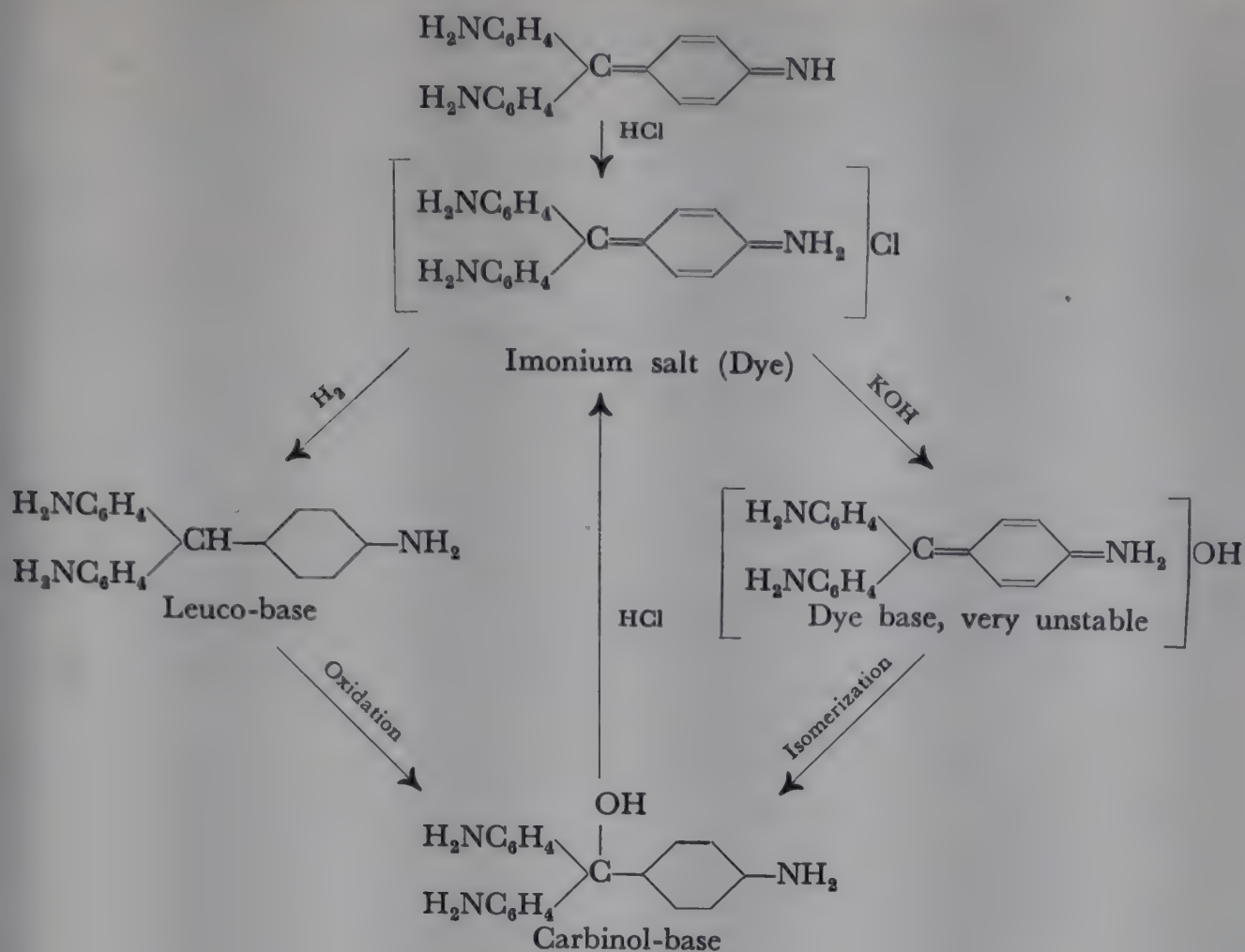


These two substances are not yet known, but phenyl derivatives of them are known: *diphenylquinomethane* or *fuchson*, and *tetraphenylquinodimethane*:



The first of these is the parent substance of a large and important class of dyes, the hydroxyfuchsones, and in the wider sense of the fuchsin, and therefore calls for special attention.

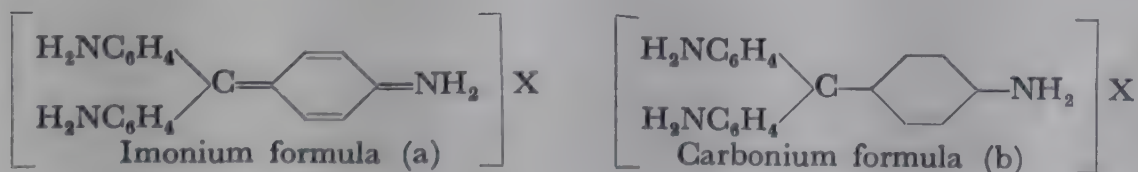
FUCHSON (diphenylquinomethane) was discovered by Bistrzycki. It is obtained by heating anisyl-diphenyl-chloromethane to 180–200°:



The introduction of the quinonoid formula for the triphenylmethane dyes goes back to Nietzki. This theory has been equally important for both the theoretical and practical development of this class of compounds. Its merit in the investigation of large groups of dyes will remain, even if it may suffer some limitation or modification in the course of time.

That unstable, true dye-bases (see the above formula) are formed as intermediate products in the conversion of fuchsone-imonium salts into the carbinol-bases is now generally recognized. Hantzsch demonstrated their existence by conductivity measurements. If the dye salt is treated with an equimolecular amount of alkali, it first forms a solution which, like ammonium hydroxide, conducts the current well. This conductivity decreases rapidly, however, as the rearrangement into the pseudo-base (carbinol compound) proceeds.

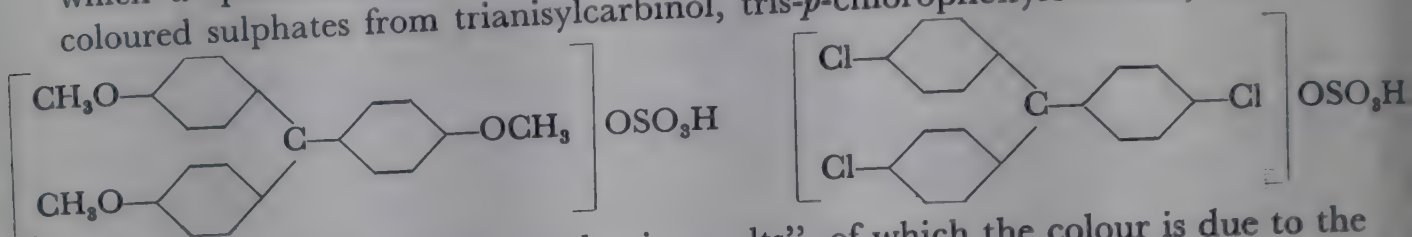
On the other hand, opinions on the *structure* of the dye-salts and the dye-bases are divided. According to the older view, they are true ammonium compounds. The only way of formulating them in this case so as to satisfy the valencies, is to regard them as quinonoid compounds (formula a). In more recent times, however, the view that they are carbonium-salts or bases (formula b) has been supported by various arguments (Fierz, Hantzsch). In this case the positive ion need not have a quinonoid structure:



The problem resolves itself into whether the carrier of the positive charge in these compounds is nitrogen or carbon.

It is quite possible that in the dye-salts and dye-bases of the triphenylmethane dyes, in one case the nitrogen, and in other cases the carbon gives up an electron, and thus becomes the bearer of the charge of the positive ion (see also p. 484).

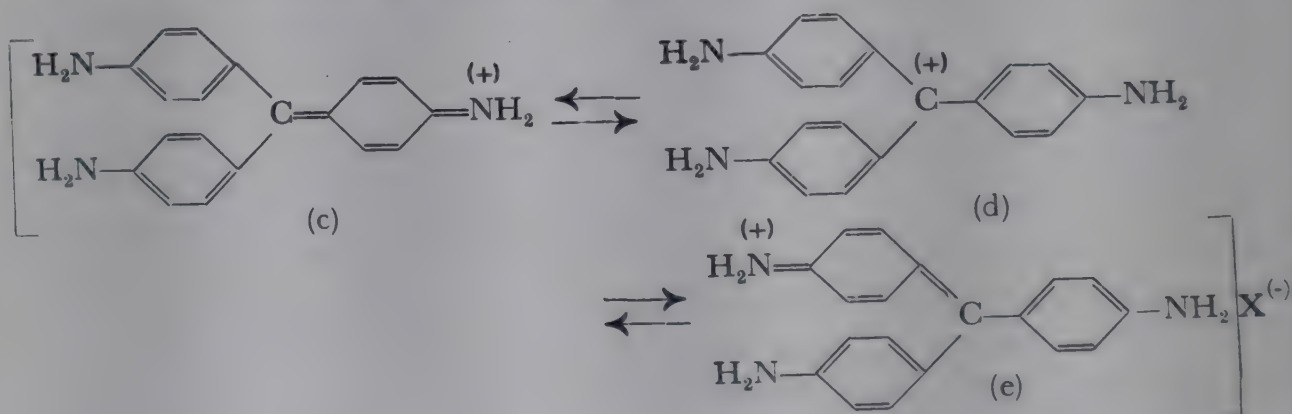
The work of Baeyer shows that also salts of triarylcarbinol compounds, in which a quinonoid structure is impossible, can possess colour. He prepared coloured sulphates from trianisylcarbinol, tris-*p*-chlorophenylcarbinol, etc.



Undoubtedly these are "carbonium salts", of which the colour is due to the strongly unsaturated state of the molecule. This must be related to the fact that the fourth "carbonium valency" is very much weakened by the combination of that carbon atom with three phenyl radicals. In agreement with this view tri-(biphenyl)-carbinol, $(C_6H_5C_6H_4)_3COH$, and its substitution products in which the affinity of the carbinol C-atom is even more taken up because of the larger organic radicals, give coloured salts more readily than triphenylcarbinol.

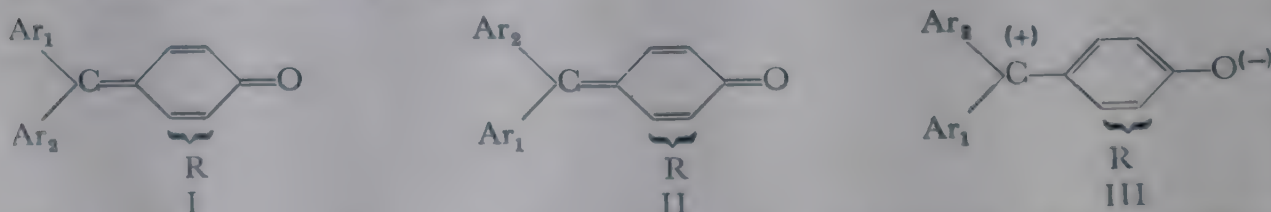
In what follows the triphenylmethane dyes will be written in the quinonoid "imonium" form, which is still that most commonly used.

According to the modern electronic formulation, the dyestuff cations are regarded as being mesomeric; they can exist in the electronic formulations (c), (d), and (e). The formulæ (c) and (e) correspond to the classical quinonoid formulation, whilst (d) corresponds to the "carbonium" or "carbenium" formulation favoured by Dilthey and Wizinger.



All these formulæ are equally correct, since they represent different possible states of a mesomeric substance.

How difficult is the decision in such problems of constitution is shown, for example, by an investigation of Bockemüller, who showed that asymmetric fuchsone derivatives occur in *cis-trans* isomeric forms I and II:

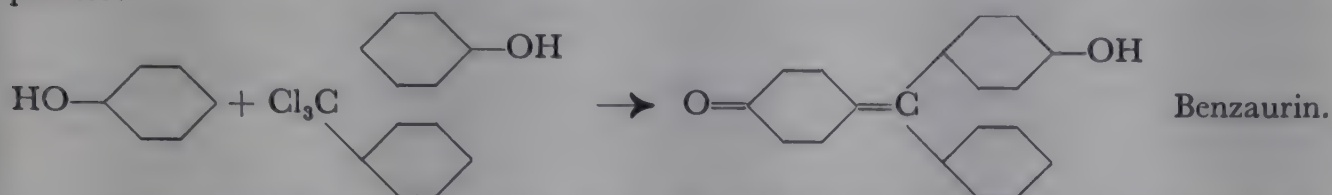


This isomerism can only occur in the case of a quinonoid structure of the compounds, and excludes the benzenoid formulation (of the type shown at III).

Hydroxy-derivatives of fuchsone

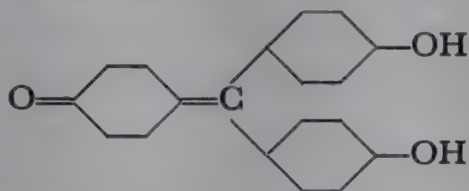
This class of compounds is also known as the *aurin* or *rosolic acid* dyes.

BENZAURIN is formed by fusing together benzotrichloride and two molecules of phenol:

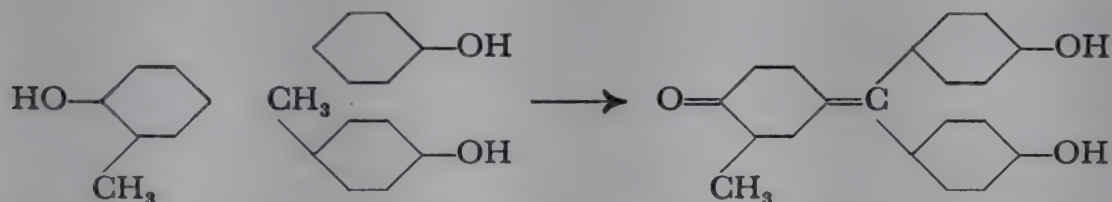


The compound is yellow-red, and dissolves in alkalis with a violet colour. It has no technical use.

AURIN is formed by heating phenol with concentrated sulphuric acid and oxalic acid, the latter providing the central carbon atom (as carbon dioxide). It can also be obtained from pararosaniline through the diazonium compound. The yellow-brown substance dissolves in alkalis giving a fuchsin-coloured solution. The sodium salt is used for dyeing wall-paper, and ordinary paper.

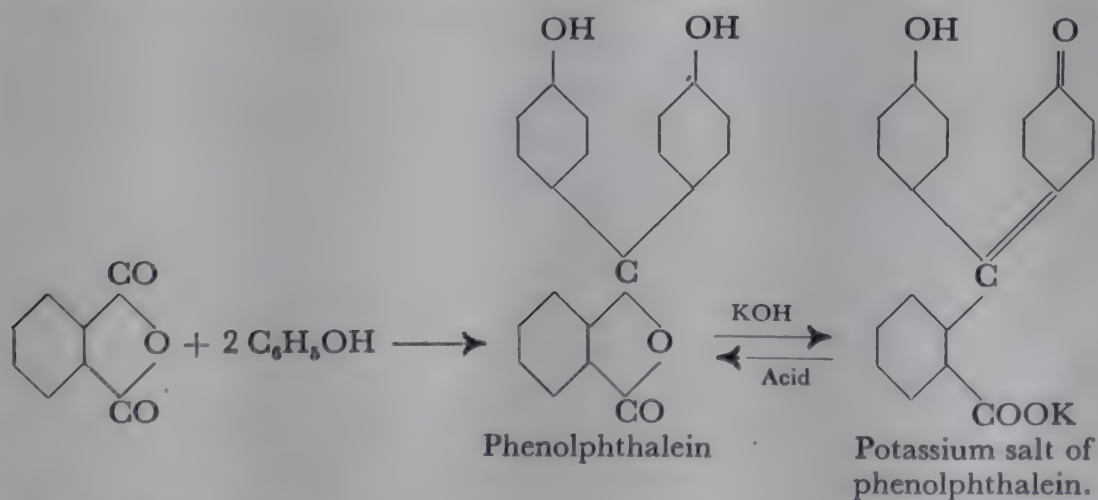


ROSOLIC ACID, a methyl-derivative of aurin, possesses very similar properties to the latter. It is obtained by boiling diazotized fuchsin (see p. 613), or by fusing phenol, *o*-cresol, and *p*-cresol with arsenic acid:



The free compound is yellow, and its alkali-metal salts violet. For this reason it finds use as an indicator.

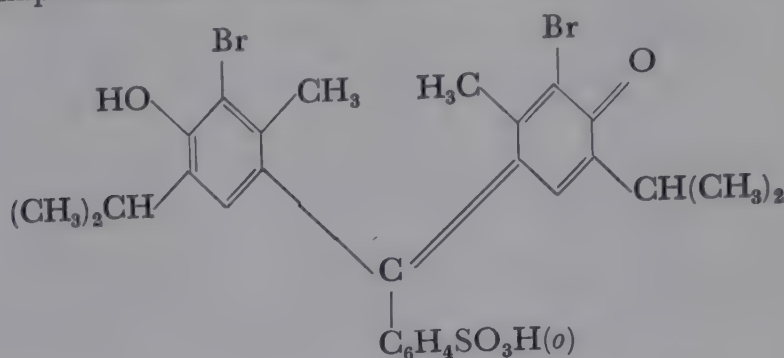
PHENOLPHTHALEIN. On heating phthalic anhydride with phenol and concentrated sulphuric acid or tin tetrachloride, the colourless phenolphthalein, is obtained. Its red alkali-metal salts have a quinonoid structure and may be regarded as carboxyl-derivatives of benzaurin:



The compound is an indicator much used in acidimetry. It is used in medicine as a purgative. Its tetraiodo-derivative has been recommended as a substitute for iodoform ("nosophene").

The esters of phenolphthalein have, like the salts, a quinonoid structure. Hence, they are coloured (yellow) (see also p. 487).

Related to phenolphthalein is dibromothymolsulphophthalein, or **BROMOTHYMOBLUE**, which is of importance as an indicator in acidimetry:



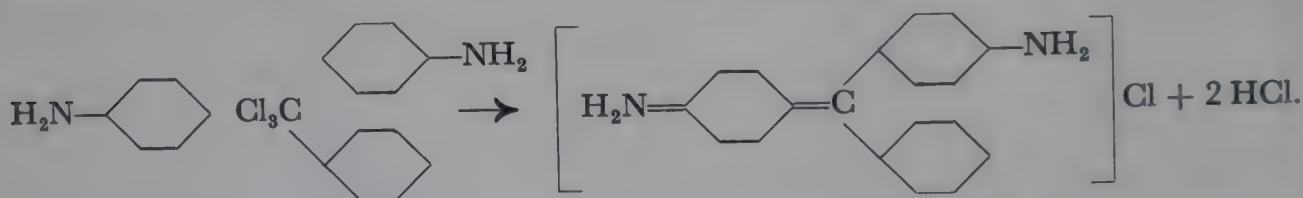
Fuchsonimonium dyes

Two important classes of dyes are derived from fuchsonimine:

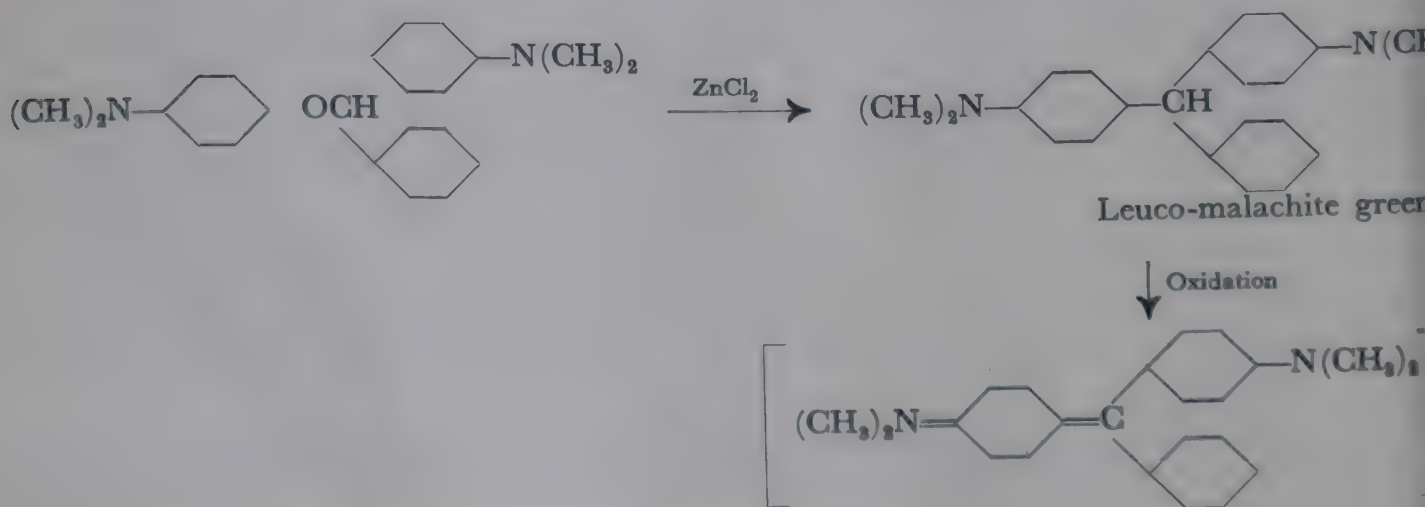
- Monoamino-fuchsonimonium salts, or *Malachite green dyes*;
- Diamino-fuchsonimonium salts, or *fuchsin dyes*.

(a) Malachite green class.

DÖBNER'S VIOLET is the simplest dye in this group. It is formed by the action of benzotrichloride on aniline, but has no technical interest:

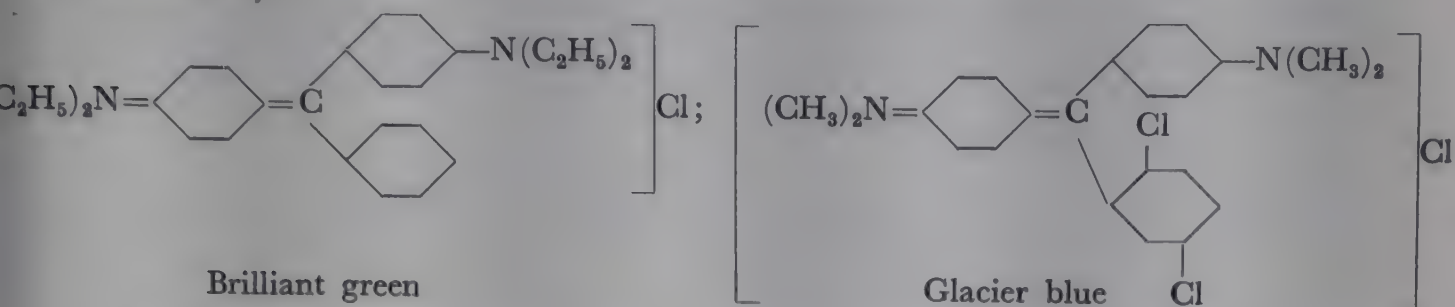


MALACHITE GREEN. The synthesis of this compound, which was discovered by O. Fischer, is carried out by condensing benzaldehyde with two molecules of dimethylaniline, under the action of hydrochloric acid or zinc chloride. The first reaction product is leuco-malachite green, which is converted into the dye by oxidation in acid solution with manganese dioxide or lead dioxide:



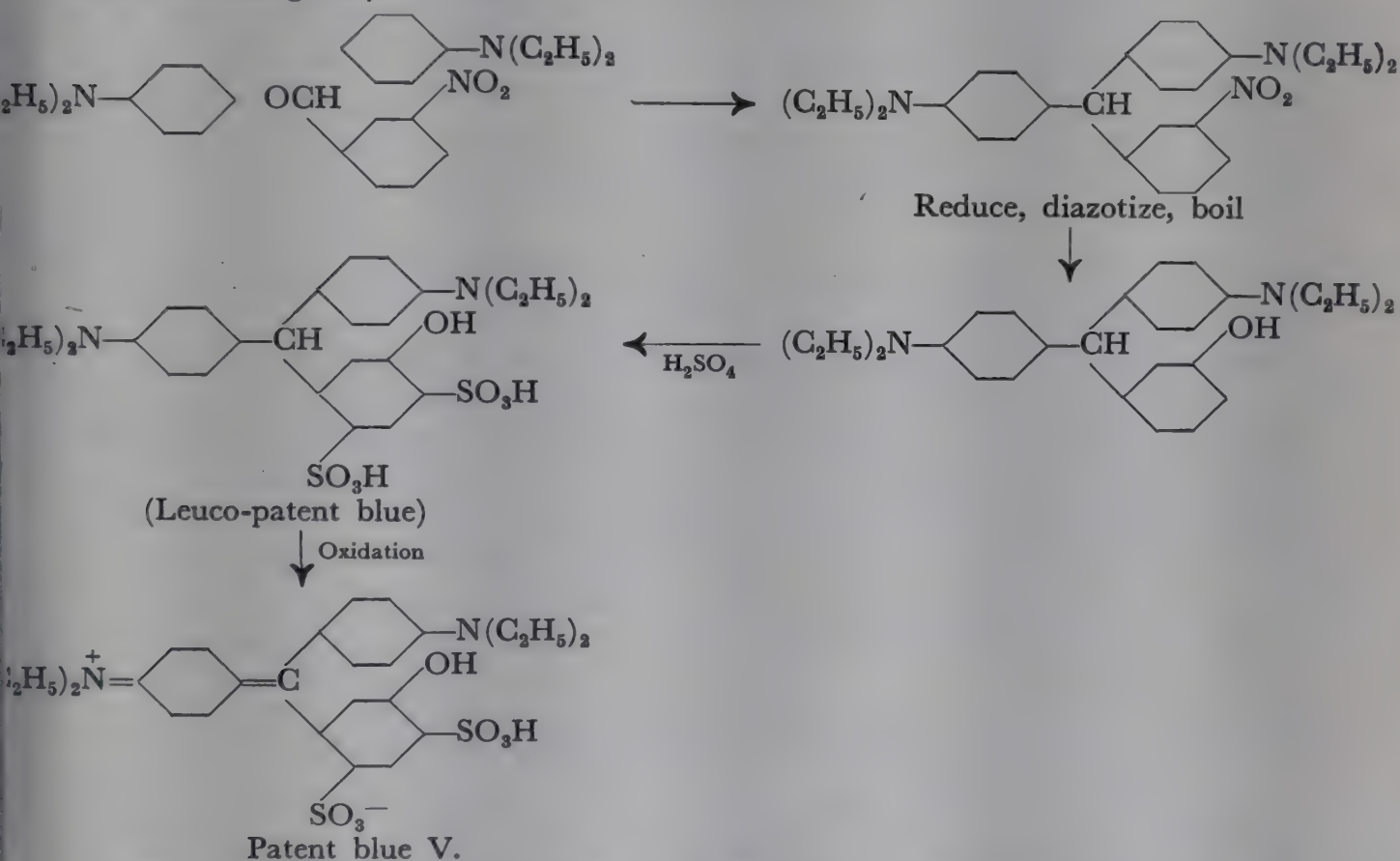
The dye comes on to the market as the oxalate, and as the double salt of the chloride with zinc chloride. Malachite green dyes tannin-mordanted cotton a deep, rich green. It is also used in silk dyeing.

The somewhat more yellowish *Brilliant green*, and a chlorinated Malachite green, *Glacier blue* (from dichlorobenzaldehyde and dimethylaniline) are made in a similar way:



All these Malachite green dyes are not very fast to alkalis, since they isomerize in the presence of hydroxyl ions into the colourless carbinol-bases. In this respect the various *Patent blues*, sulphonated Malachite green dyes, are essentially better.

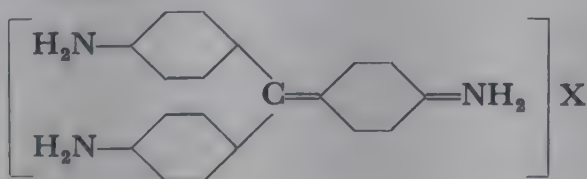
PATENT BLUE V. This is made from diethylaniline and *m*-nitrobenzaldehyde in the following way:



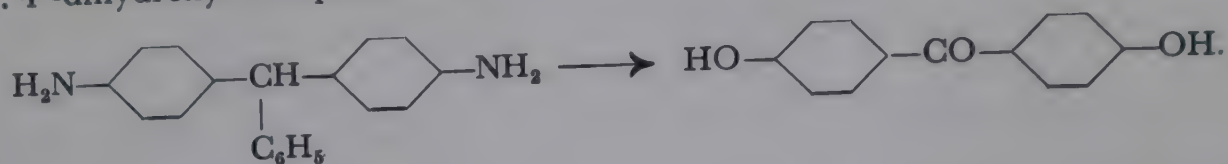
The compound is an internal salt. It dyes a pure blue, moderately fast to alkalis, and is valued as a dye for wool and silk.

(b) Fuchsin class.

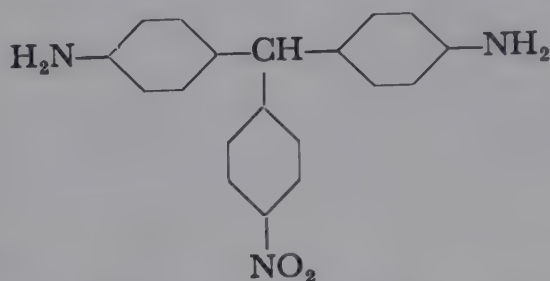
PARAFUCHSIN OR PARAROSANILINE.



The honour of having largely elucidated the constitution of the fuchsin dyes falls to E. and O. Fischer. They showed first that parafuchsin on reduction gives a leuco-base, the diazo-compound of which, when acted upon by alcohol, yields triphenylmethane. Parafuchsin was thus shown to be a derivative of triphenylmethane. The positions of the amino-groups were determined by the following considerations: Bis-(*p*-aminophenyl)-phenylmethane, obtained by condensation of benzaldehyde with aniline, contains the two NH_2 -groups in the *p*-position to the central methane carbon atom, since it is converted, on fusion with alkali, into 4 : 4'-dihydroxybenzophenone:

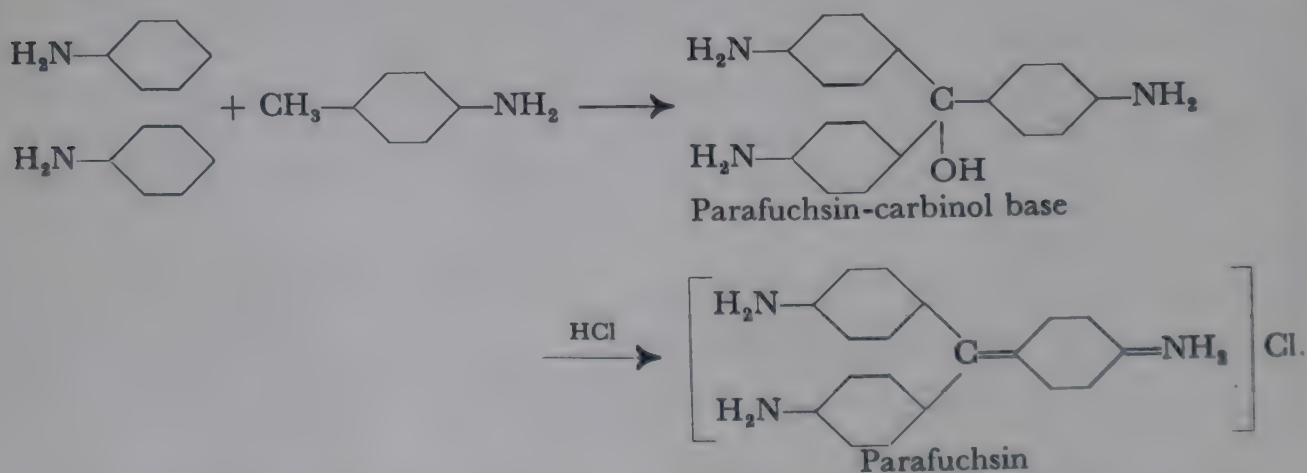


If, in place of benzaldehyde, *p*-nitrobenzaldehyde is condensed with aniline, 4 : 4'-diamino-4''-nitrotriphenylmethane must be formed in an analogous manner:

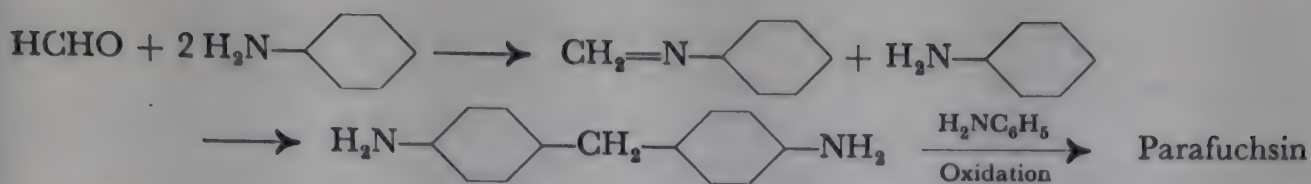


This compound gives, on reduction, leuco-pararosaniline, the constitution of which is thus made clear.

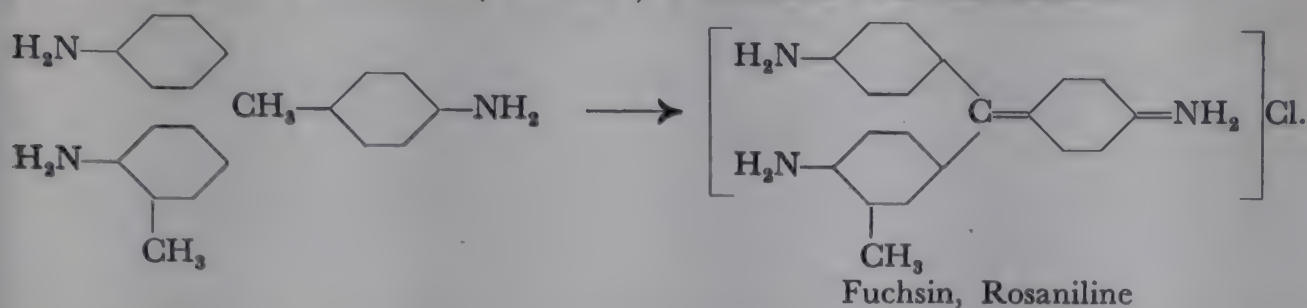
Pararosaniline is prepared commercially by the oxidation of a mixture of 2 mols. of aniline and 1 mol. of *p*-toluidine with arsenic acid (older process); or with nitrobenzene (newer process due to Coupier). The *p*-toluidine furnishes the central methane carbon atom of the dye. Probably the toluidine becomes first oxidized to the aldehyde during the process:



Another method of preparation (new fuchsin process, Homolka) starts from aniline and formaldehyde. The anhydroformaldehydeaniline thus produced is converted by heating with aniline and aniline hydrochloride into *p,p'*-diaminodiphenylmethane. If the latter is treated with aniline and an oxidizing agent, direct condensation occurs to parafuchsin:



FUCHSIN, or ROSANILINE, is a methyl homologue of parafuchsin and is produced by similar methods to the latter. Usually a mixture of equal parts of aniline, *p*-toluidine, and *o*-toluidine ("red oil") is oxidized with nitrobenzene:



Fuchsin and parafuchsin form crystals with a metallic greenish lustre, which dissolve in water and alcohol with a deep red colour. Both compounds dye silk and wool, as well as tanned cotton a brilliant red. However, on account of the slight fastness of the colours, the use of fuchsin has greatly decreased. On the other hand, it is used for the manufacture of phenylated derivatives (Aniline blue, etc.).

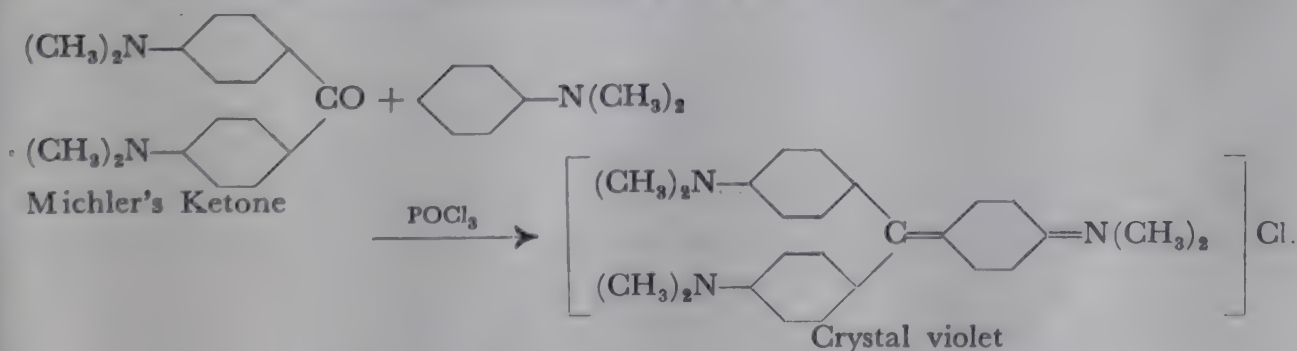
METHYL VIOLET. If the hydrogen atoms of the amino-groups in fuchsin and parafuchsine are replaced by methyl, ethyl, or phenyl radicals, the colour is displaced towards the violet and blue. The greatest deepening of the colour is produced by phenyl groups.

By Methyl violet is understood a mixture of lower and higher methylated fuchsins. Several brands of different degrees of methylation are available commercially. They were formerly made by the alkylation of fuchsin (with methyl alcohol and hydrogen chloride). Now a product is produced, which consists essentially of a pentamethylparafuchsin (Dahlia B), by oxidation of dimethylaniline with copper sulphate. The central methane carbon atom necessary for the formation of the dye is here supplied by decomposed molecules of dimethylaniline.

Methyl violets (especially the pentamethyl-derivative) are still used for dyeing silk, wool, and tanned cotton. The colours are not, however, fast to light. They are also used in the manufacture of inks, and in medicine to a limited extent as disinfectants ("Pyoctanin").

CRYSTAL VIOLET is hexamethylpararosaniline hydrochloride. It derives its name from its ready ability to crystallize.

It is prepared from dimethylaniline and phosgene. The tetramethyldiaminobenzophenone, or Michler's ketone, obtained from them is fused with dimethylaniline and phosphorus oxychloride, thus giving Crystal violet, via the carbinol-base:

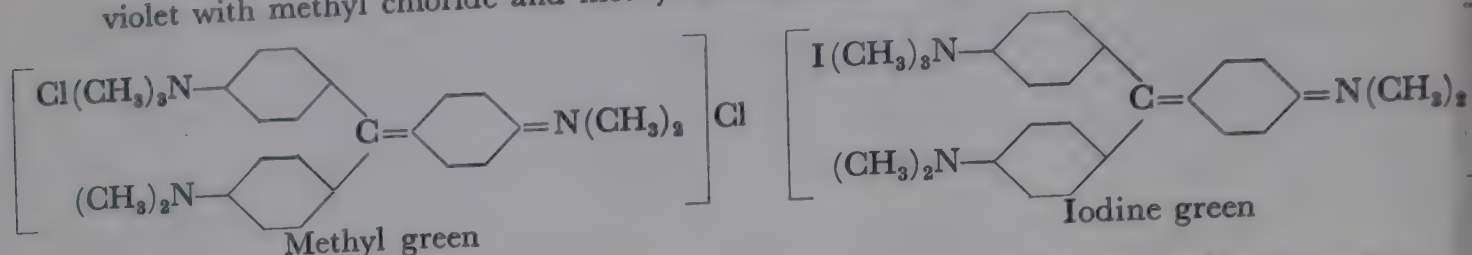


FUCHSONE DYES

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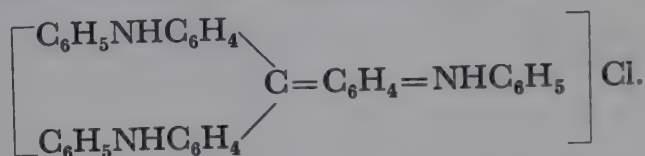
The dye gives a bluish violet colour on wool and tannined cotton, but is not very fast to light.

METHYL GREEN and IODINE GREEN are two dyes produced by methylation of Methyl violet with methyl chloride and methyl iodide, respectively:

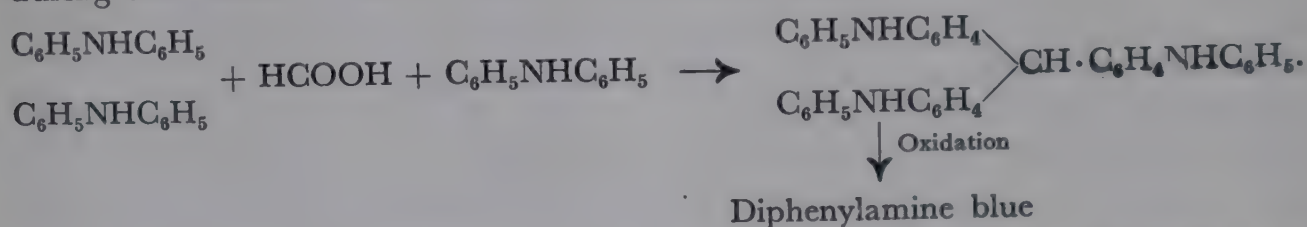


At one time they were fairly widely used, but have now been entirely replaced by Malachite green and other compounds. However, they are of some interest from the theoretical point of view. It is clear from their formulæ that they both contain a fully alkylated, and hence coordinately saturated, amino-group, which, on account of its complete saturation, can no longer act as an auxochrome. The violet colour of the Methyl violets is thus displaced to green, and the dye takes on the shade of the Malachite green group, which compounds also have only two amino-groups acting as auxochromes.

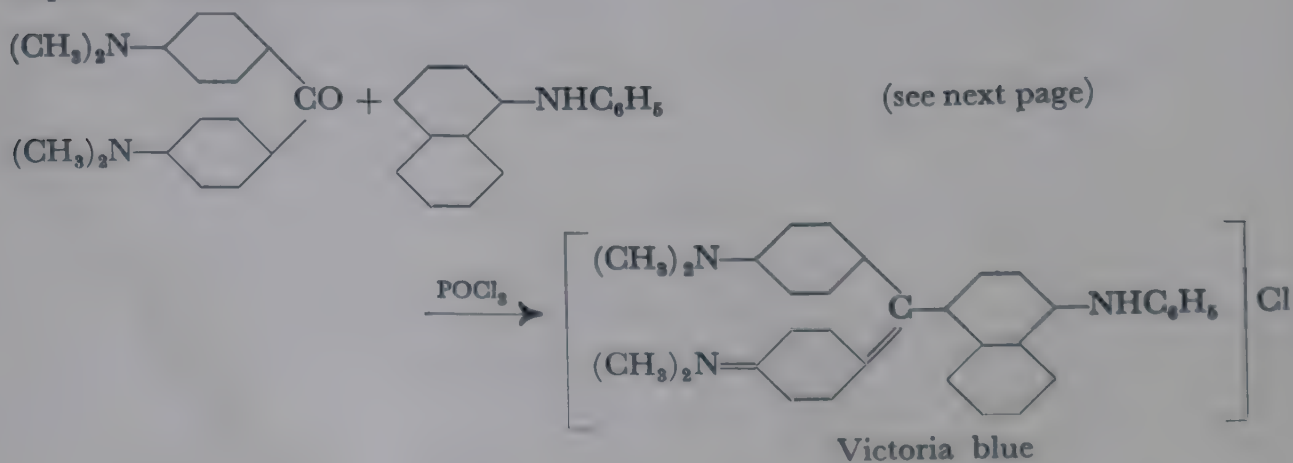
ANILINE BLUE, *triphenylfuchsin hydrochloride*, is made by fusing fuchsin or parafuchsin with aniline (180°), benzoic acid being the best condensing agent:



The same dye is produced, though in small yield, by heating diphenylamine with oxalic acid, and is then called "*Diphenylamine blue*" (the oxalic acid breaks down during the fusion to carbon dioxide and formic acid).



Aniline blue is only slightly soluble in water, but more readily in alcohol. It is therefore also called *Spirit blue*. It is usually used in the form of various sulphonic acid salts. The sodium salt of the monosulphonic acid is *Alkali blue*. It is chiefly used for dyeing wool. "*Water blue for silk*" is the sodium salt of the disulphonic acid, and "*Water blue for cotton*" is a mixture of the acid sodium salts of tri- and tetra-sulphonic acids of Aniline blue.



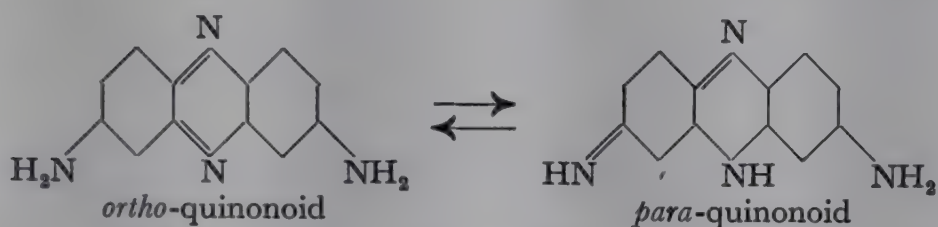
Victoria blue is a dye of the fuchsin series which contains a naphthalene nucleus. It is prepared from tetramethyldiamino-benzophenone and phenyl- α -naphthylamine on heating with phosphorus oxychloride (see previous page).

It is used fairly extensively for dyeing cotton (also when not tannined), wool, and silk.

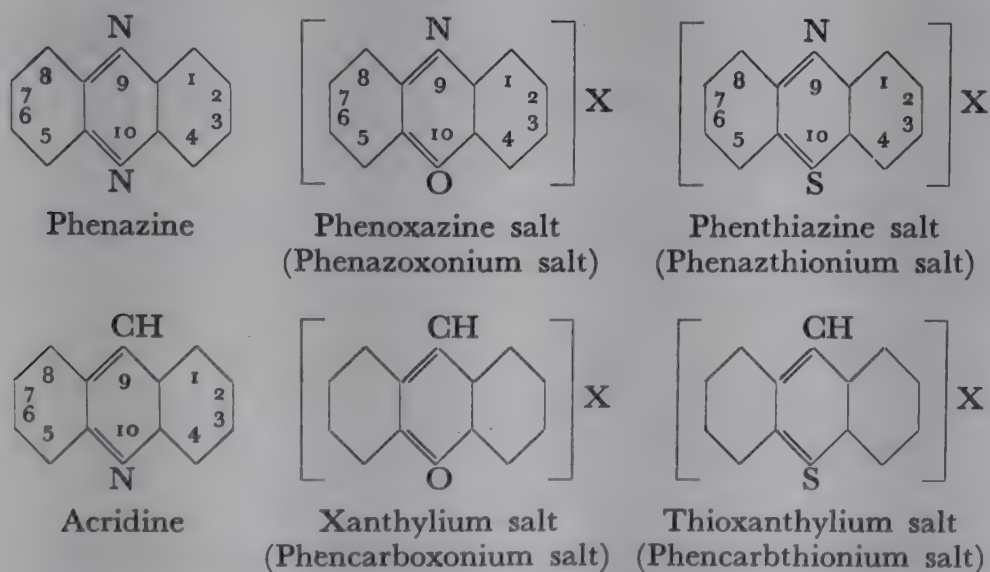
CHAPTER 49

QUINONE DYES WITH CLOSED RINGS

The dyes considered in this chapter may be regarded as derivatives of *o*-benzoquinone. Many of them can, however, be written in the *para*-quinonoid form. It is seldom possible to distinguish unequivocally between the two formulations. It must rather be supposed that the two are equally justified, and that in one case the *ortho*-, in the other the *para*-quinonoid formula gives a satisfactory picture of the behaviour of the compound concerned. Thus, the following types, for example, are tautomeric:



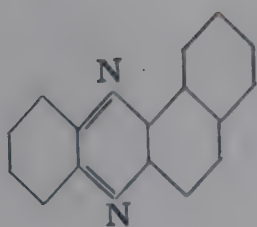
The quinonoid dyes with closed rings dealt with here may be derived from the following parent substances:



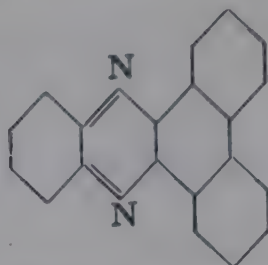
A. Phenazine dyes¹

In this class of dyes are included not only those compounds derived from phenazine itself, but also those derived from naphthophenazine, phenanthrophenazine, or naphthazine nuclei:

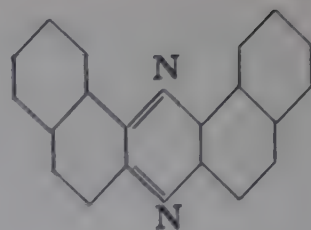
¹ See also F. KEHRMANN, *Gesammelte Abhandlungen*, Leipzig, (1922-25).



Naphthophenazine



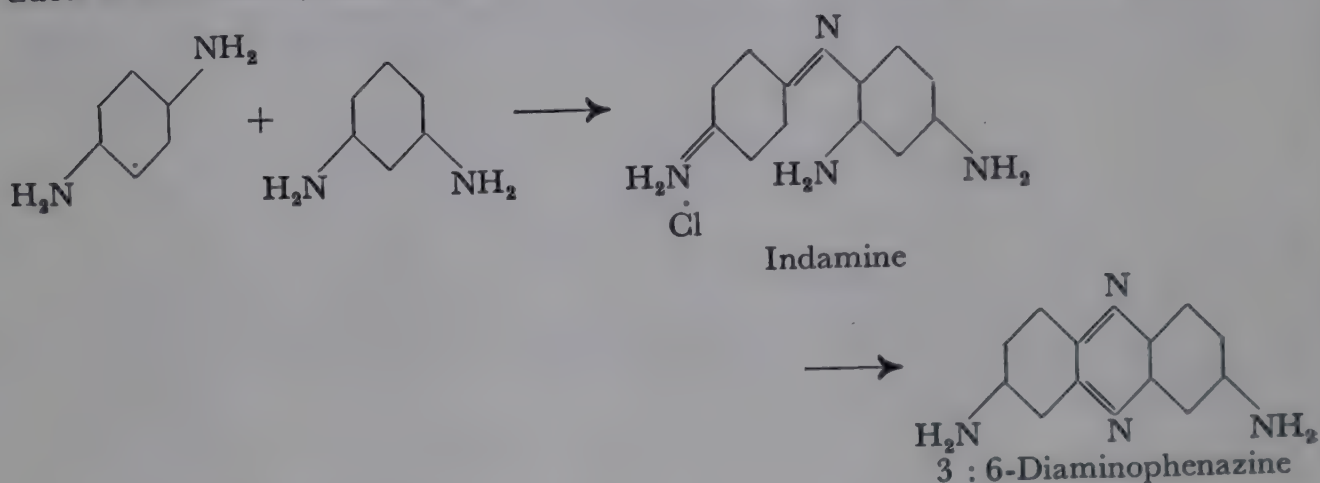
Phenanthrophenazine



Naphthazine

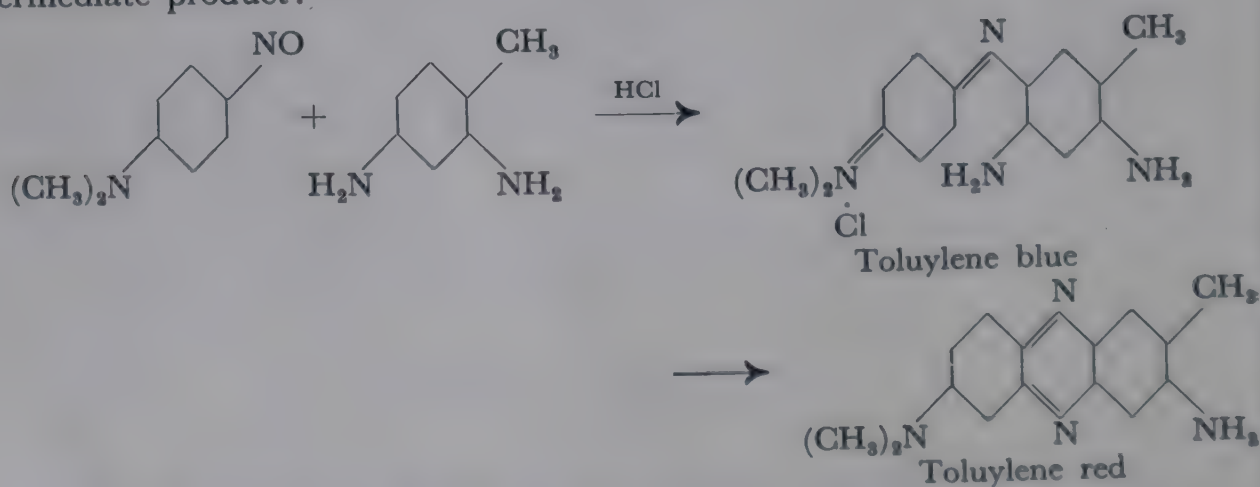
EURHODINES, EURHODOLS. Although O. N. Witt understood by eurhodines monoaminophenazines, and by eurhodols monohydroxyphenazines, these terms are, as a rule, now used generally for aminophenazines and hydroxyphenazines in general.

Eurhodines are usually prepared by the oxidation of an equimolecular mixture of a *p*-diamine and a *m*-diamine in acid solution, or from nitrosodimethylaniline and a *m*-diamine. Thus, 3:6-diaminophenazine is obtained from *p*-phenylenediamine and *m*-phenylenediamine. Indamines are intermediate products in all these syntheses, and can therefore also be used as starting materials:



3 : 6-Diaminophenazine is yellow. Its mineral acid salts have a red colour. It has no practical use as a dye.

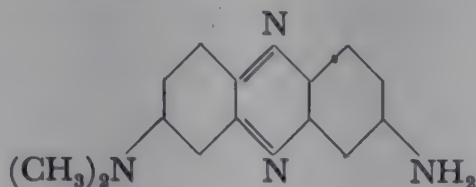
NEUTRAL RED, or TOLUYLENE RED (Witt) is formed from nitrosodimethylaniline hydrochloride and *m*-toluylenediamine. The indamine *Toluylene blue* is an intermediate product:



Toluylene red is also formed by disproportionation of toluylene blue, which takes place on boiling an aqueous solution of the latter (p. 585). The leuco-product is formed at the same time.

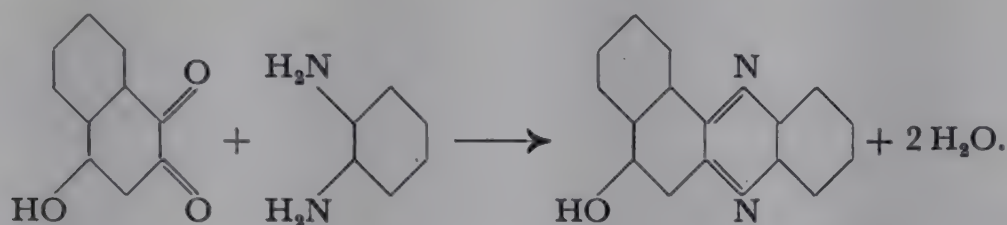
The dye-base has an orange-yellow colour; the salts are violet. It dyes tannin-mordanted cotton a not very fast violet-red.

NEUTRAL VIOLET,

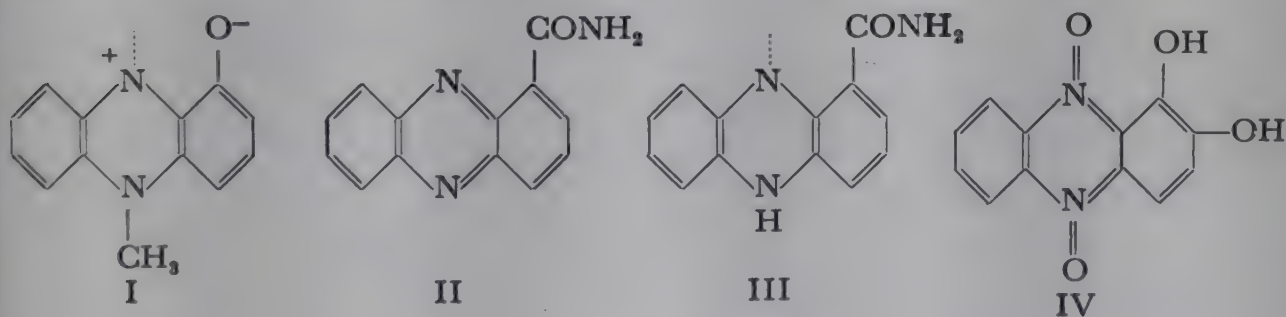


is formed by oxidation of dimethyl-*p*-phenylenediamine and *m*-phenylenediamine. It dyes tanned cotton a red-violet.

EURHODOLS (hydroxyphenazines) have no technical interest. As phenols and azine-compounds they have both acidic and basic properties. Eurhodols are obtained by hydrolysis of eurhodines, which for this purpose are heated to 180° with hydrochloric acid, or by direct synthesis from hydroxy-*o*-quinones and *o*-diaminobenzenes, e.g.



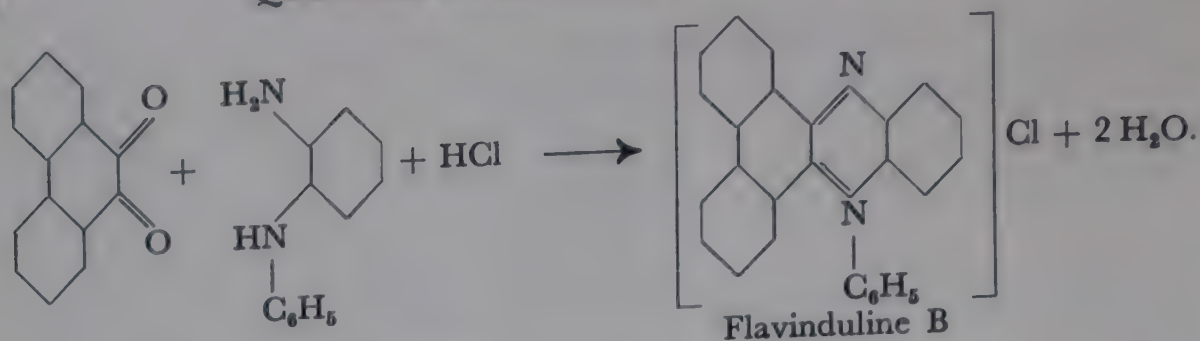
The colours of various bacteria are due to phenazine dyes. According to the investigations of F. Wrede and L. Michaelis, *pyocyanine*, the pigment of *B. pyocyaneus*, has the semiquinonoid formula I. The most important degradation product of this substance is α -hydroxyphenazine. The compound can also be prepared synthetically. The pigment of *B. chlororaphis*, the green *chlororaphine*, is, according to Kögl, a derivative of phenazine- α -carboxylic acid amide. It is synthetically formed when equimolecular quantities of dihydrophenazine- α -carboxylic amide and phenazine- α -carboxylic amide (II) are mixed. It may be considered as a quinhydrone or a semiquinone (III). The pigment of *Chromobacterium iodinum* is regarded by Clemo as a dihydroxy-phenazine-di-N-oxide (IV):



Phenylphenazonium salts. The phenylphenazonium dyes form a large, and very well developed class of substances, which also includes the first organic dye to be produced synthetically, *mauveine* (Perkin, 1856). Only comparatively few compounds of this group are now used in any considerable quantity for dyeing.

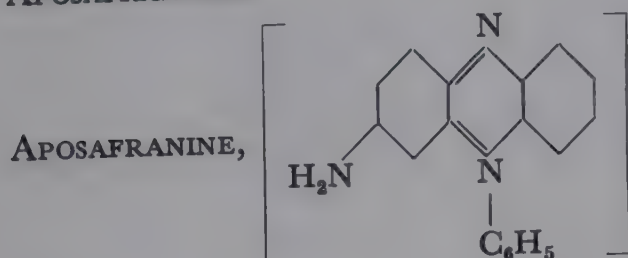
Most phenylphenazonium dyes are diamino-derivatives, and less often monamino-derivatives. The first are called *safranines*, and the second *aposafranines*. Flavinduline B does not contain an amino-group.

FLAVINDULINE. This is prepared from phenanthrenequinone and phenyl-*o*-phenylenediamine in acid solution:



The yellow-brown dye finds a limited use in cotton printing.

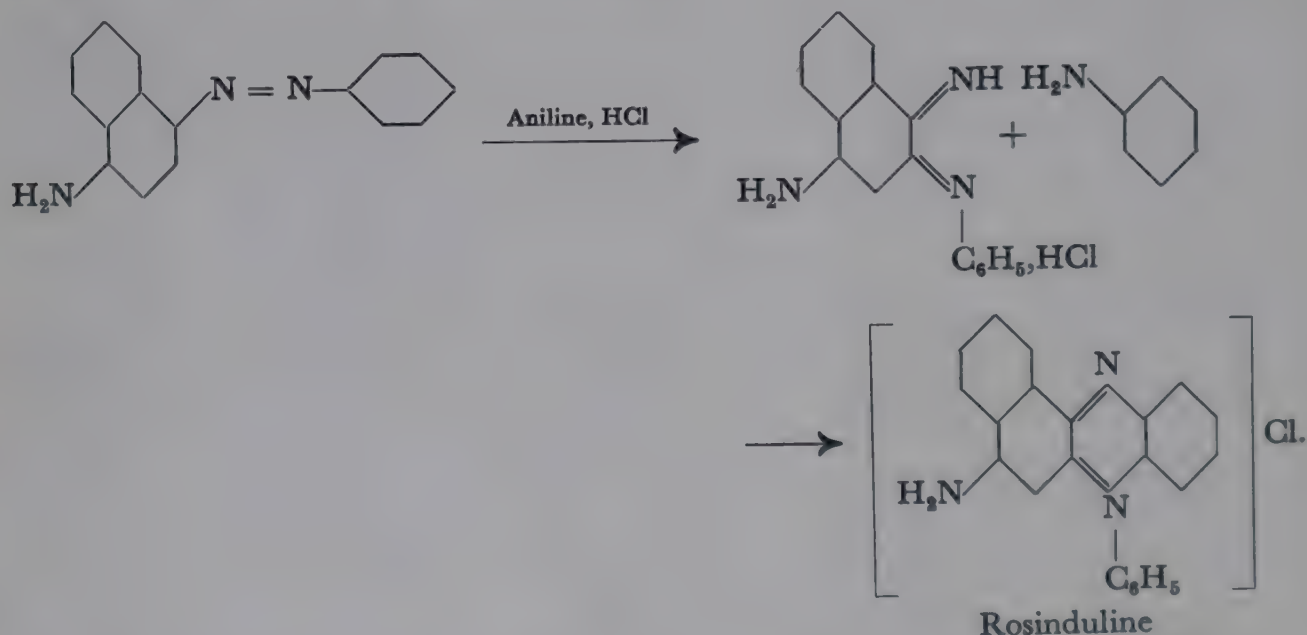
APOSAFRANINES.



Cl is produced from safranin by elimination of an amino-group. It has no technical value.

ROSINDULINE. The name rosinduline is used for the monoamino-derivatives of phenylnaphthophenazonium salts. By displacement of the NH_2 -group a large number of isomeric compounds can be predicted, which have nearly all been prepared by Kehrmann and his co-workers.

Ordinary rosinduline (Otto Fischer) is obtained technically from naphthylamine-azobenzene, which is heated to about 170° with aniline, aniline hydrochloride, and alcohol. The reaction is bound up with a rearrangement, the course of which is shown by the following scheme:

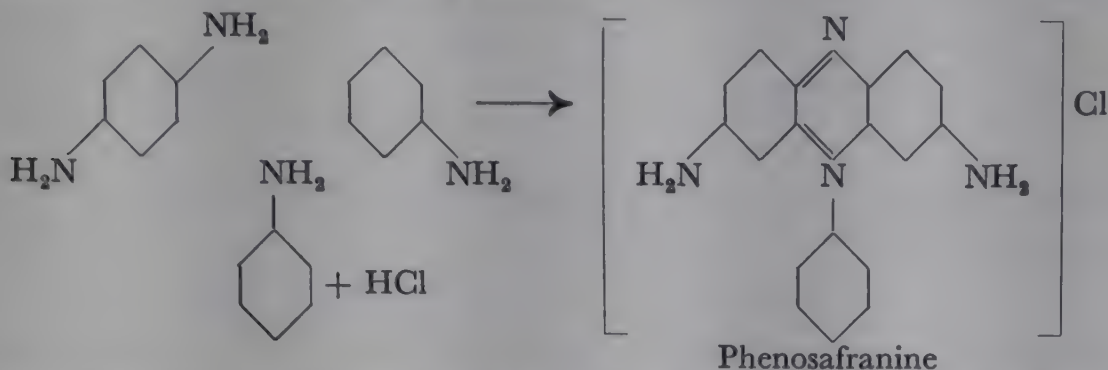


The rosinduline salts are red. In concentrated sulphuric acid the dye dissolves with a green colour. It itself has only slight importance. More important is the sodium salt of the disulphonic acid of N-phenylrosinduline, which comes on to the market under the name *Azocarmine G*, and is used for dyeing silk as well as wool.

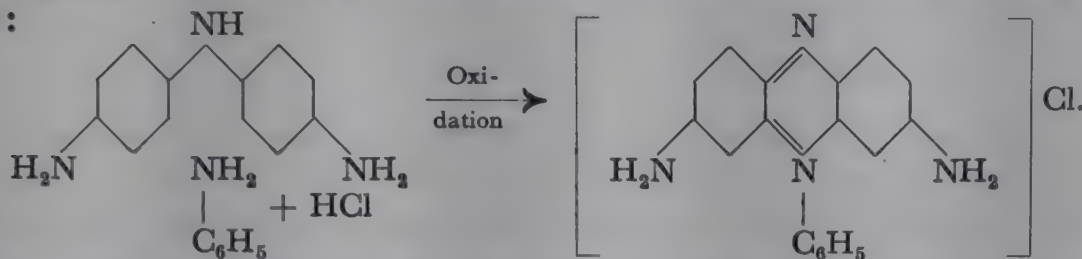
SAFRANINES. The safranines, diamino-derivatives of the phenylphenazonium salts, in spite of their insufficient fastness to light, have, even today, a limited use as dyes for tanned cotton, silk, and also, in part, wool. Their monacid salts have red to violet colours. In addition they can also form di- and tri-acid

salts, if water is excluded, the former being blue, and the latter green. It is possible that they are derived from different quinonoid systems (*ortho* and *para*).

PHENOSAFRANINE is prepared either by oxidation of *p*-phenylenediamine and two molecules of aniline in acid solution:

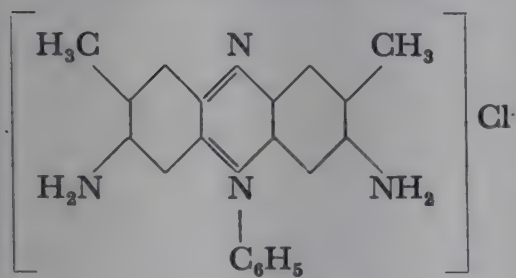


or from diamino-diphenylamine and aniline, which are oxidized in the presence of acid:

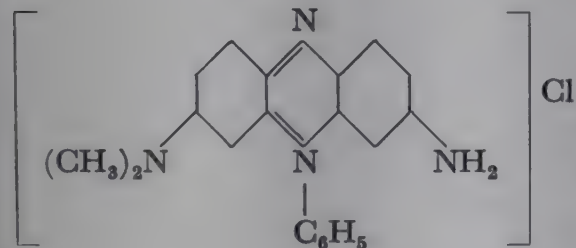


These methods serve also, *mutatis mutandis*, for the preparation of other safranine dyes.

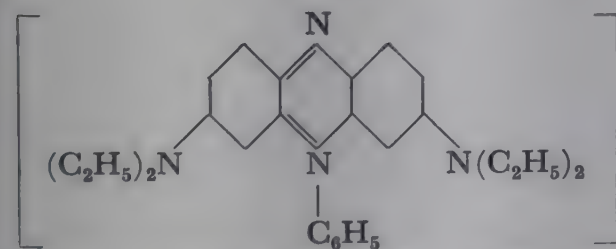
Phenosafranine dyes a red colour, but it has no practical interest.



TOLUSAFRANINE (Brilliant safranine) is made from *p*-toluylenediamine, *o*-toluidine, and aniline. It gives a fairly fast, bluish red colour on tanned cotton and silk, and is much used.

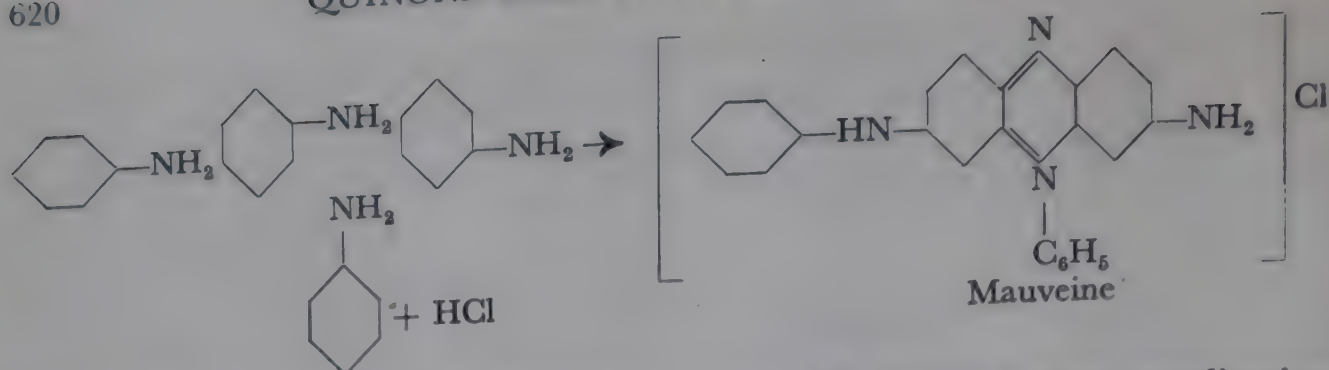


FUCHSIA, synthesized from dimethyl-*p*-phenylenediamine and aniline. It is a valuable cotton dye, fast to washing and light.

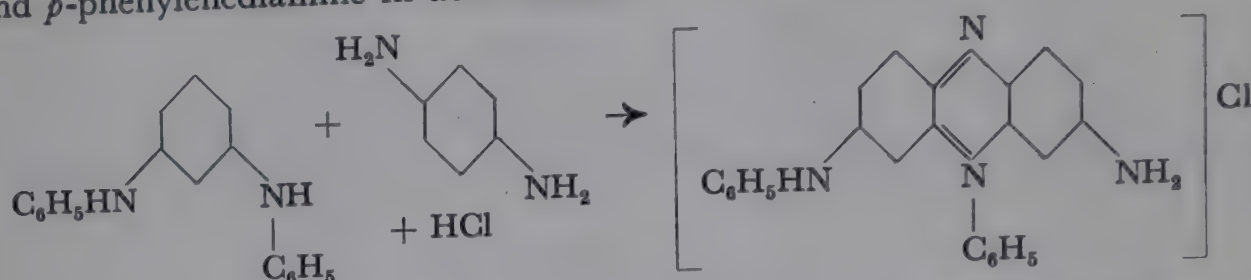


AMETHYST VIOLET. This violet silk dye, which has a beautiful fluorescence, may be made by oxidizing a mixture of diethyl-*p*-phenylenediamine, diethylaniline, and aniline.

MAUVEINE (Perkin's mauve). Mauveine was prepared by Perkin, in the expectation of obtaining quinine, by the oxidation of impure aniline. It was the first synthetic dye to be prepared (1865). His product was not homogeneous, but contained as its chief constituent N-phenylphenosafranine (and its homologues). It must have been formed by the condensation of four molecules of aniline in the following manner:

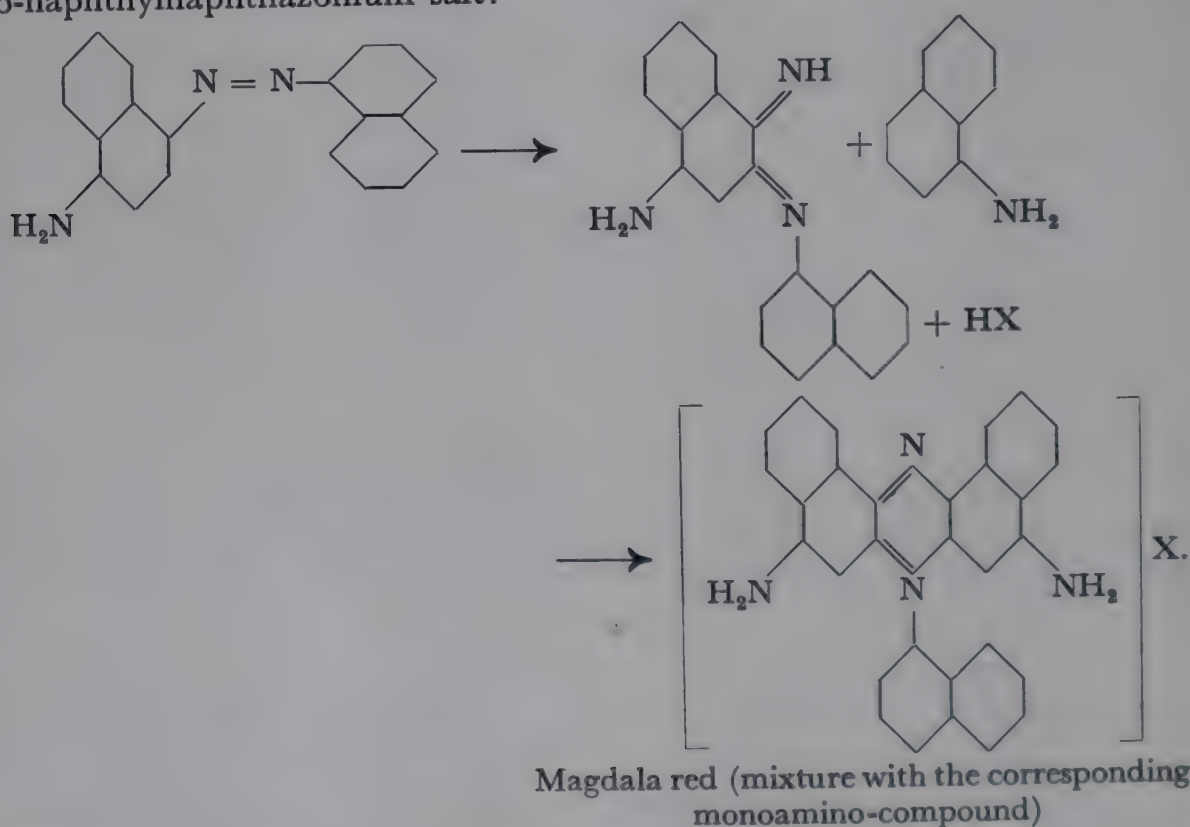


Mauveine is better obtained by joint oxidation of diphenyl-*m*-phenylenediamine and *p*-phenylenediamine in acid solution:



The dye has scarcely any practical interest nowadays. Some homologues of mauveine are, however, still used in dyeing.

MAGDALA RED is formed on fusing α -naphthylamine-azonaphthalene with α -naphthylamine acetate, and consists of a mixture of a monoamino- and a diamino-naphthyl-naphthazonium salt:

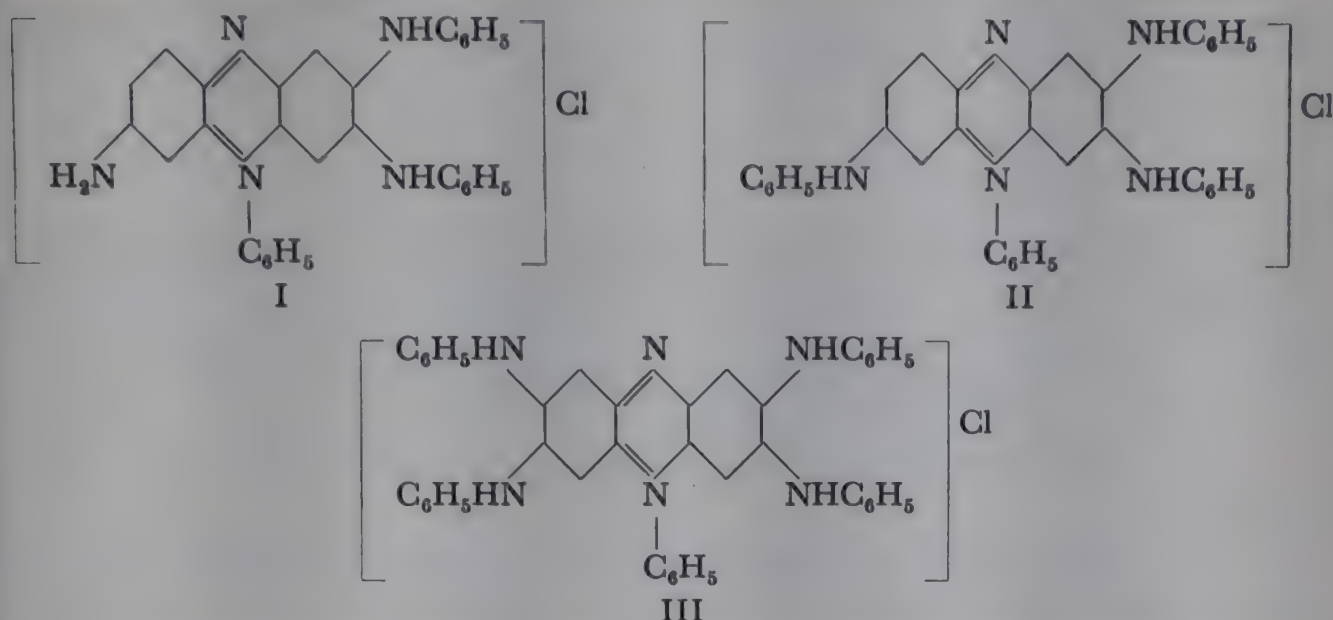


The dye is very difficultly soluble in water, but dissolves more readily in alcohol. It is used for dyeing silk, on which it produces rose shades.

INDULINE. The indulines are phenylated polyaminophenylphenazonium salts. They are produced in the so-called induline fusion, i.e. the heating together of *p*-aminoazobenzene, aniline, and aniline hydrochloride, which gives a mixture of various components.

The first induline that can be separated from the melt when the fusion is

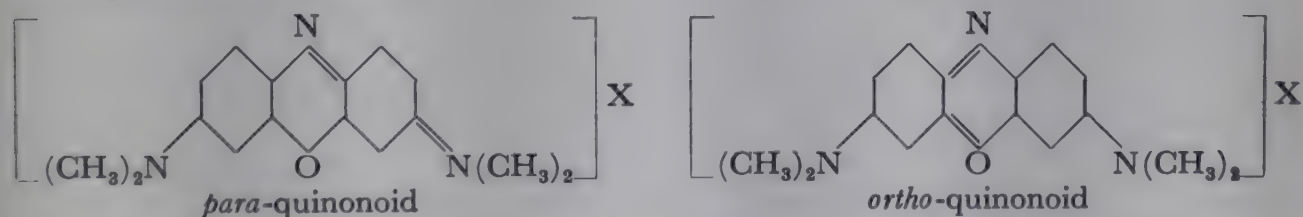
prematurely stopped is Indamine blue (I), which, on further heating with aniline hydrochloride, condenses to higher phenylated indulines (II) and (III) with elimination of ammonia:



Most indulines, both in the form of bases and of salts, are insoluble in water, but are soluble in alcohol. Water-soluble preparations are obtained by sulphonating the dyes. Spirit-soluble indulines are used for dyeing tanned cotton, and the water-soluble ones (sodium salts of the sulphonic acids) are suitable for wool and silk dyeing. The shade of the dye varies with the composition of the product, and is displaced from violet-blue to green-blue (highest stage of phenylation). A solution of indulines in acetylated glycerol (acetin) is a substitute for indigo.

B. Oxazine dyes

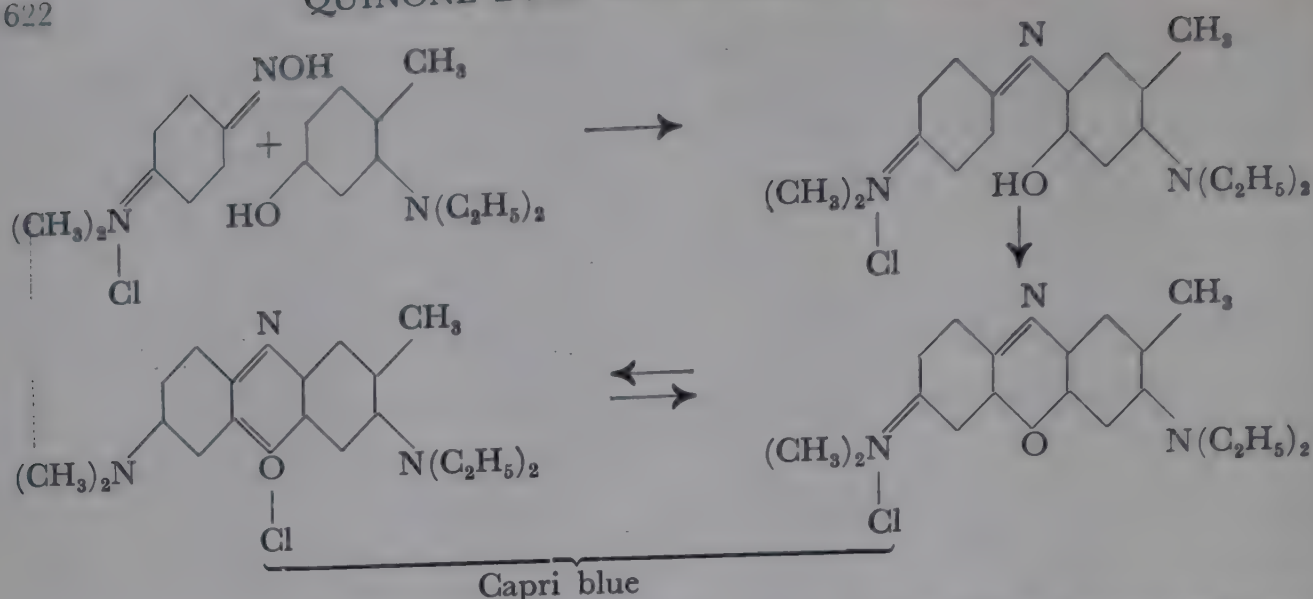
The dyes derived from phenoxazine $\left[\text{C}_6\text{H}_4 \begin{array}{c} \text{N} \\ \diagup \quad \diagdown \\ \text{O} \end{array} \text{C}_6\text{H}_4 \right] \text{X}$ are regarded sometimes as ammonium, and sometimes as oxonium salts. The first view (Bernthsen, O. Fischer) leads to a *para*-quinonoid formula, the latter (Kehrmann) to an *ortho*-quinonoid formula:



At present no definite evidence is available upon which a decision can be made between the two formulæ. The whole point of the problem is whether a nitrogen or the oxygen atom carries the charge of the positive oxazine dye ion. Reliable methods of determining this are not at present available.

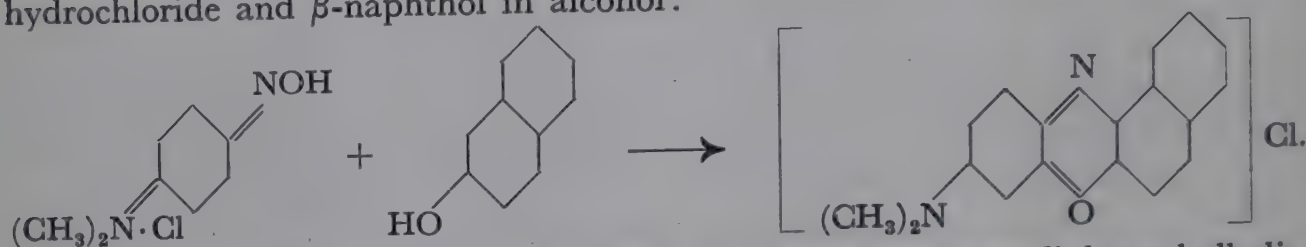
These oxazines are prepared by the condensation of nitrosodimethylaniline or nitrosophenols with dialkyl-*m*-aminophenols. Gallic acid, pyrogallol, and resorcinol, may be used in place of the latter in the preparation of certain oxazines.

CAPRI BLUE is made from nitrosodimethylaniline hydrochloride and *m*-diethylamino-*p*-cresol:



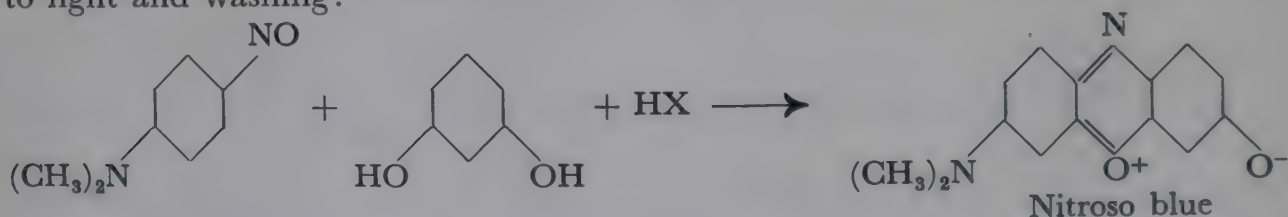
The colours of Capri blue on tannined cotton are valued on account of their fastness.

MELDOLA BLUE (NEW BLUE R) is formed by warming nitrosodimethylaniline hydrochloride and β -naphthol in alcohol:

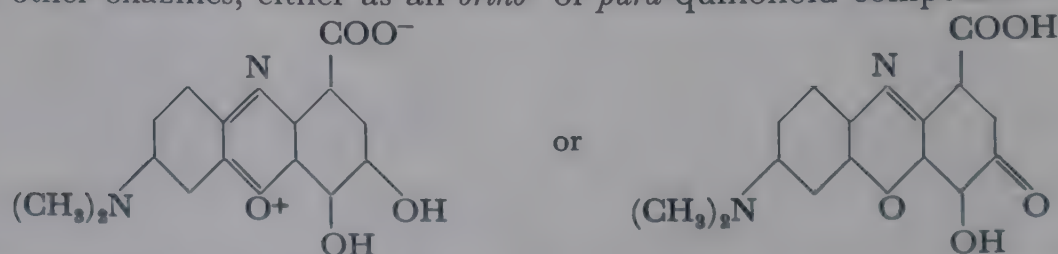


It dyes tannined cotton an indigo-blue, but is not very fast to light and alkalis.

NITROSO BLUE is usually produced on the fibre, e.g. cotton, which is printed with nitrosodimethylaniline hydrochloride, resorcinol, and tannin, and the dye is produced by exposing the fabric to steam. The indigo-blue lake is fairly fast to light and washing:

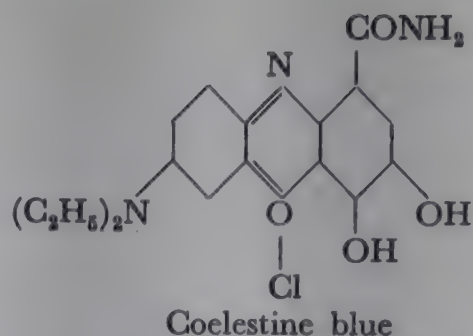
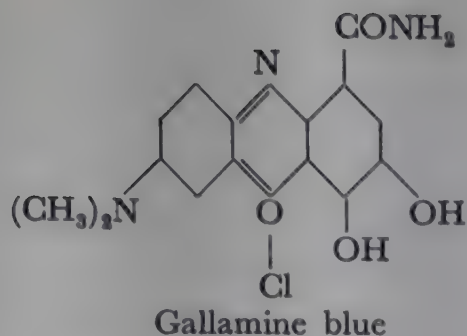


GALLOCYANINE. On heating nitrosodimethylaniline hydrochloride with gallic acid the important mordant dye gallocyanine is produced. It can be considered, like the other oxazines, either as an *ortho*- or *para*-quinonoid compound:

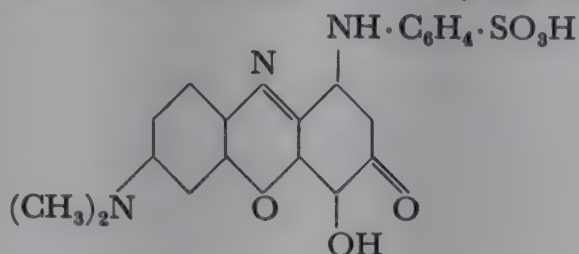


Gallocyanine hydrochloride forms needles with a green lustre, which dissolve in water to give a violet-coloured solution. It is often used with metallic mordants, especially as the chrome lake, and gives violet shades of considerable fastness.

GALLAMINE BLUE is a derivative of gallocyanine, prepared from nitrosodimethylaniline and gallamide. The corresponding diethyl compound is *Coelestine blue*. Both are mordant dyes:



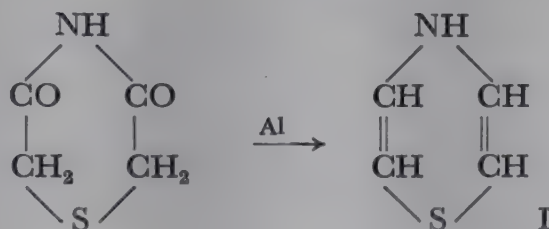
On fusing galloxyaniline with aromatic amines, there appears to be a replacement of the carboxyl by an amino-radical. Thus, if aniline is used, and the product is subsequently sulphonated, *Delphine blue B* is formed. It dyes chromed cotton and wool, and is fast to light. It is usually represented by the following constitutional formula :



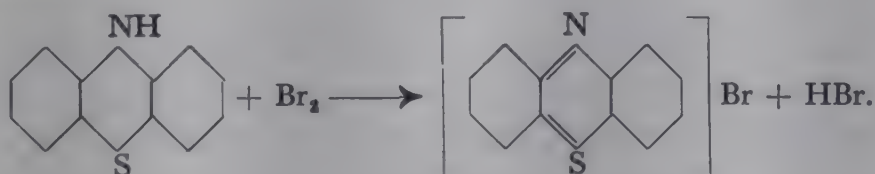
(According to other views the aniline radical does not take the place of the carboxyl group, but combines with it to form an anilide.) The *phenocyanines*, important dyes in calico printing, are obtained from galloxyaniline and phenols (e.g. resorcinol) on heating, the carboxyl group being replaced.

C. Thiazine dyes

The simplest *1:4-thiazine* (I) can be prepared from thiodiglycolic acid imide by reduction with aluminium at an elevated temperature; it is a colourless liquid boiling at 77°:



The thiazine dyes are derived from the phenazothionium base (phen-thiazine base), which according to Kehrman, is obtained from thiodiphenylamine and bromine:

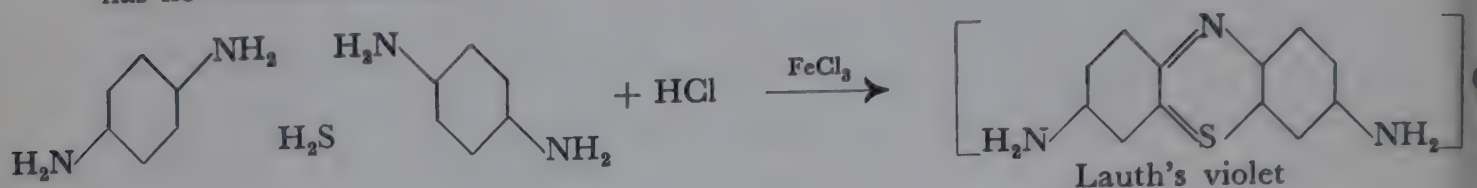


Thiodiphenylamine, a colourless substance which crystallizes well and melts at 180°, is formed by heating diphenylamine with sulphur or sulphur monochloride:



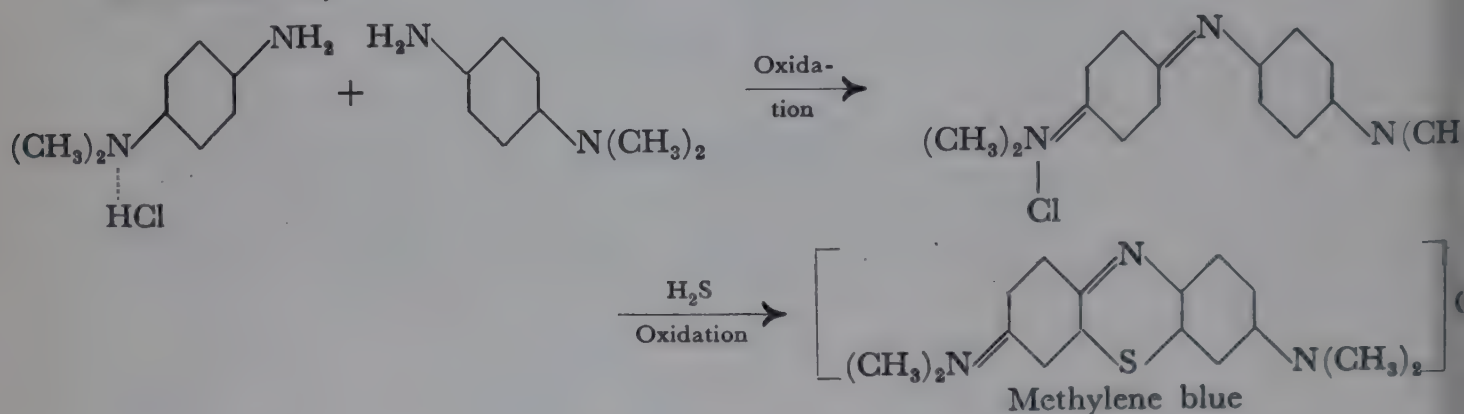
The most important dyes of the thiazine class are the 3:6-diaminophen-thiazines. The first member of this class was obtained by Lauth by joint oxidation of *p*-phenylenediamine and hydrogen sulphide with ferric chloride in acid solution. This method is also applicable to other *p*-diamines with a free NH_2 -group, and proceeds so readily that it serves for the detection of hydrogen sulphide, and of *p*-diamines, a violet or blue coloration indicating their presence.

LAUTH'S VIOLET (1876), made from *p*-phenylenediamine and hydrogen sulphide has no technical interest:

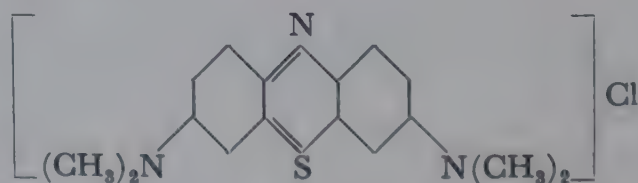


METHYLENE BLUE, the tetramethyl derivative of the above-mentioned dye, has, in contrast to the latter, practical importance. Its synthesis goes back to Caro (1876), and its constitution was elucidated by Bernthsen.

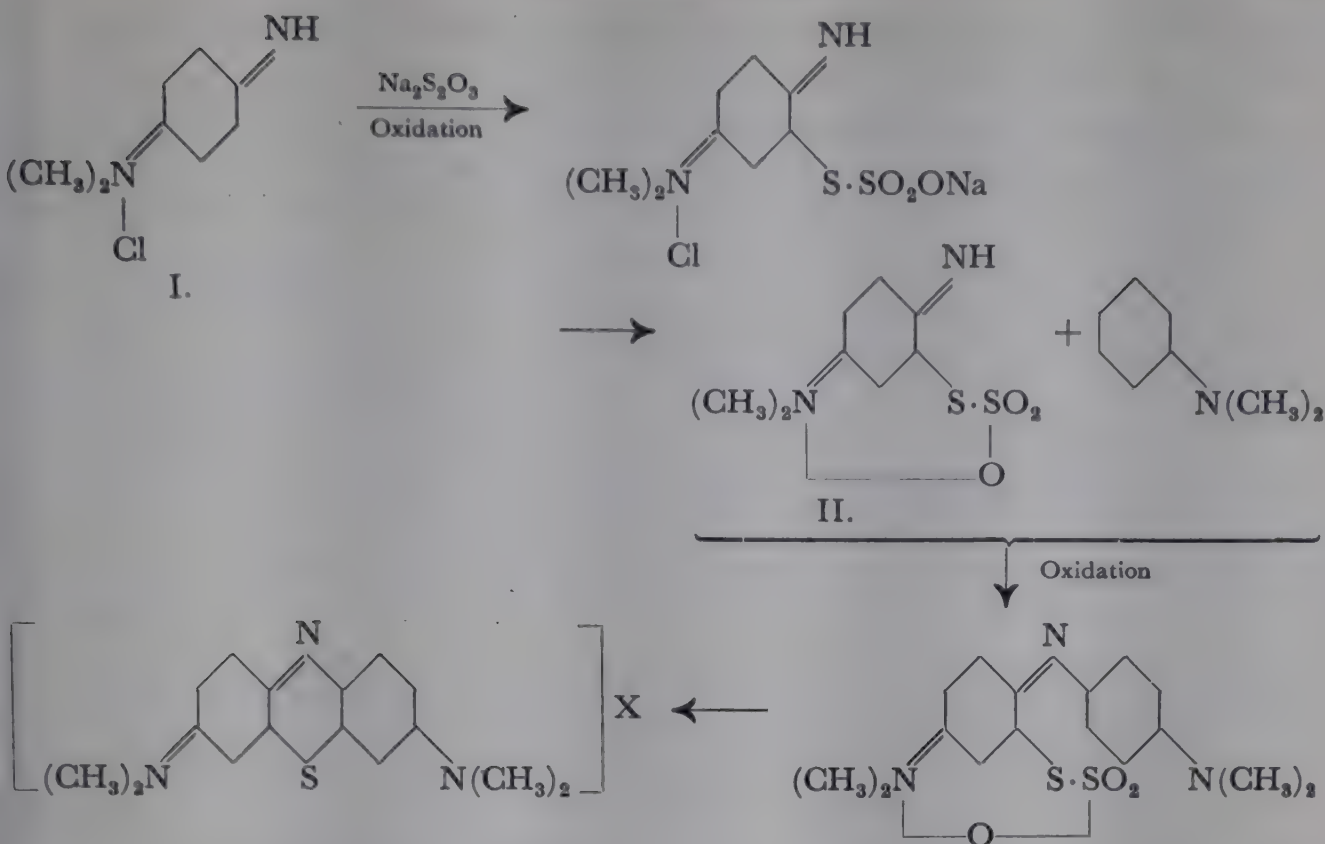
The first synthesis of Methylene blue is founded on Lauth's reaction, and consists in the oxidation of *as*-dimethyl-*p*-phenylenediamine and hydrogen sulphide with ferric chloride. An indammonium salt (*Bindschedler's green*, p. 584) is formed intermediately, which then condenses with the hydrogen sulphide to give the thiazine dye:



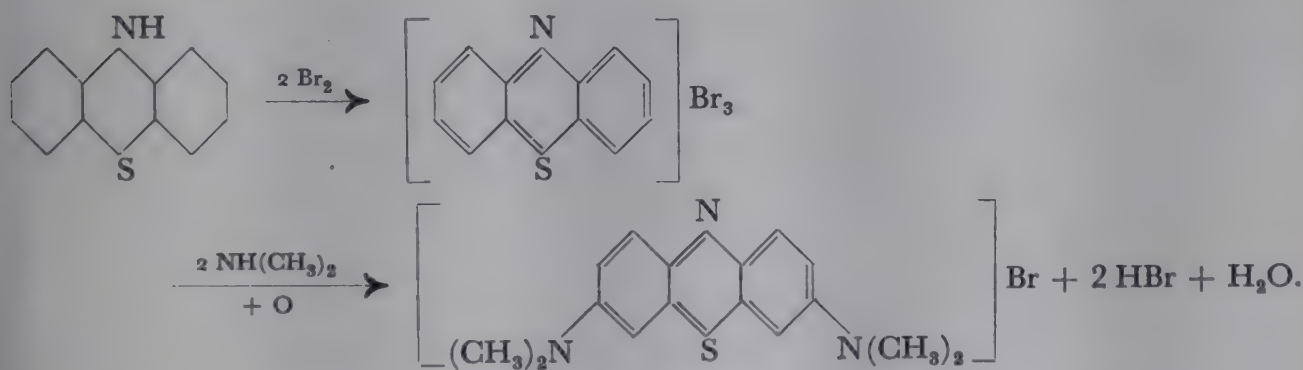
As with the oxazine series, the *ortho*- and *para*-quinonoid formulations for the Methylene blue dyes are also equally justified. The formula of Methylene blue may therefore also be written:



The old Caro synthesis of Methylene blue was later replaced by one due to Bernthsen, in which the starting materials are 1 mol. dimethyl-*p*-phenylenediamine, 1 mol. dimethylaniline, and sodium thiosulphate. The quinonoid oxidation product of the dimethyl-*p*-phenylenediamine (I) combines with the sodium thiosulphate, and gives compound (II), the internal salt of an acid, under the influence of oxidizing agents. This can be isolated in the form of compact crystals. If it is further oxidized (with potassium dichromate) together with dimethylaniline, Methylene blue is formed:



Finally, there is a third synthesis of Methylene blue due to Kehrman, which has no technical importance, but deserves mention on account of the simple genetic connection it displays, between the parent substance of this class of compounds, thiodiphenylamine, and the dye. An excess of bromine acts upon thiodiphenylamine to give phenazthionium perbromide. This combines with dimethylamine to give Methylene blue. The process appears to take place in two stages. First there is addition of the amine to the quinonoid benzene nucleus, and then there is intramolecular oxidation, the perbromide group acting as oxidizing agent:



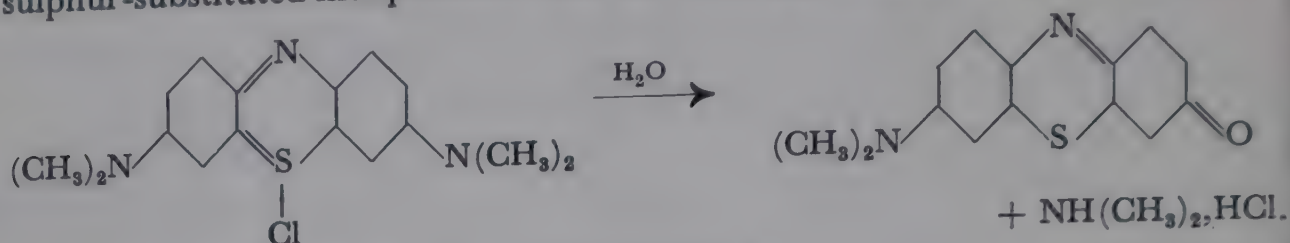
Methylene blue usually comes on to the market as the zinc chloride double salt. It is readily soluble in water giving a blue solution. It is extensively used for dyeing tanned cotton, and in calico printing, on account of the purity of its shade, and its excellent fastness to washing and chlorine (it is moderately fast to light). Wool absorbs the dye insufficiently, but silk takes the dye well.

Methylene blue is what is known as a "vital" dye, i.e. it stains deeply certain parts of the living organism, namely, the peripheral nervous system, leaving other parts colourless.

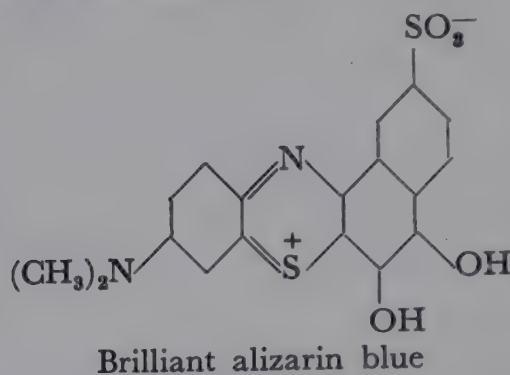
By acting upon Methylene blue in various ways, other dyes have been made. The action of nitrous acid gives *Methylene green*, which is apparently a mono-

nitro-derivative of Methylene blue. It dyes tannined cotton a fast, deep green, and is used extensively.

On heating Methylene blue with alkalis, hydrolysis occurs with the elimination of an amino-group. The reaction product, *Methylene violet*, can be regarded as a sulphur-substituted indophenol. From the dyeing point of view it is of no value:



Another dye belonging to the thiazine series is:



The chrome lake of Brilliant alizarin blue, which is very fast, finds extensive application, particularly in wool dyeing and calico printing.

D. Sulphur dyes

The sulphur dyes, substances of great technical importance, have not all the same structural basis, but belong obviously to different classes of compounds. The justification for treating them in one group is based on two points: the fact that *analogous methods of preparation* hold for all sulphur dyes, the method being the fusion of the most diverse organic substances with sulphur or sodium polysulphides, and the fact that they are all used *in the same way in dyeing*. This begins with the conversion of the insoluble dye into an alkaline reduction product by means of sodium sulphide, followed by the steeping of the fabric in this solution, and the re-oxidation to the dye on the fibre by atmospheric oxygen. It is rare to find another method of dyeing used, though primuline is an exception.

The reason for considering this class of dyes briefly at this point is because some blue and blue-black sulphur dyes are very probably complex thiazine compounds.

The first incentive for the opening up of this class of compounds goes back to 1873, when Croissant and Bretonnière, by fusing waste organic matter (sawdust, bran, etc.) with alkali sulphide obtained a product, which dyed cotton a greenish colour, and after treatment with dichromate, a brown shade. It came on to the market under the name *Cachou de Laval*.

A black dye, *Vidal black*, obtained in 1893 by Vidal on heating *p*-amino-phenol with sodium sulphide, was of much greater technical importance. It formed the direct incentive for the intensive technical study of sulphur- and alkali-polysulphide fusions. The results were soon evident in a flood of patents, in which

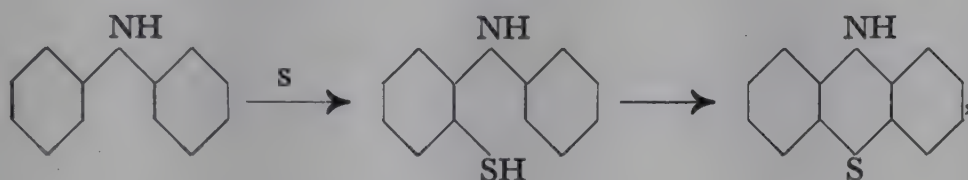
the formation of yellow, brown, green, blue, and black sulphur dyes from the most diverse organic substances was described. Many of these compounds dye cotton from a sodium sulphide (or hydrosulphite) vat with excellent fastness, and this, together with their cheapness has given them a many-sided practical application.

As already mentioned, the constitution of the majority of sulphur dyes is still not clear. Most of these amorphous, insoluble products are probably mixtures of various components. A few, such as *Immedial pure blue*, crystallize, and allow an insight into their constitution.



It appears that two large groups of sulphur dyes must be distinguished; first, the blue to blue-black dyes which belong to the thiazine type, and second, the yellow to brown dyes, which in part are derived from the heterocyclic, five-membered thiazole ring, and have their best investigated representative in *Primuline*.

Blue sulphur dyes. The first reaction products on fusing aromatic amines and hydroxy-compounds with sulphur or alkali polysulphides, appear to be mercaptans, which contain the SH-group in the *ortho*-position to the amino- or hydroxyl-radical, respectively. In the course of the fusion these are then oxidized not only to disulphides, but also, in consequence of more powerful oxidizing processes, further changes occur leading in particular to ring-closure to thiazine or thiazole derivatives.

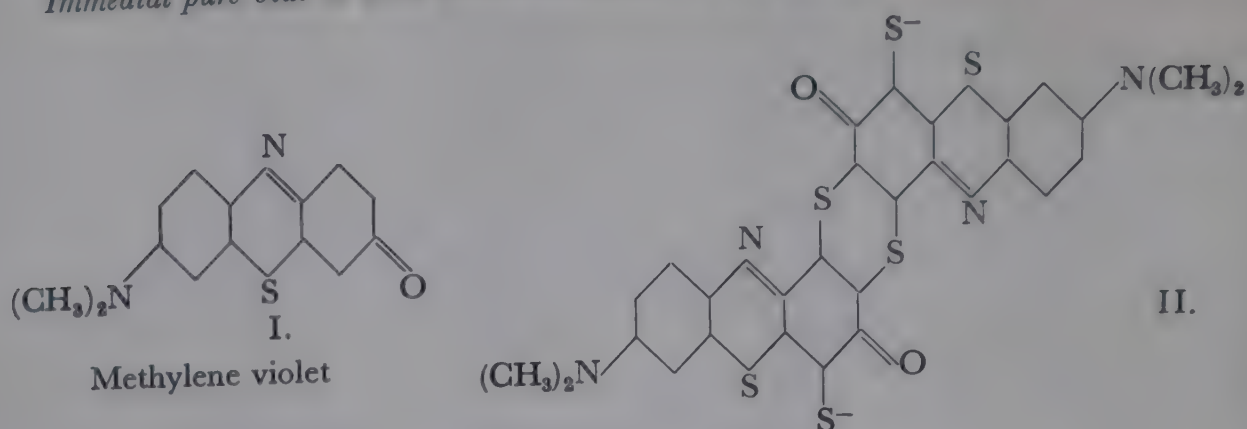
Whilst diphenylamine under these conditions is converted into thiodiphenylamine:



the sulphurization of hydroxy- and amino-derivatives of diphenylamine, indophenols, and similar substances occurs much more readily, and gives, through the introduction of several mercaptan groups, dyes containing one or more disulphide groups —S—S— , or in the reduced form, —SH groups.

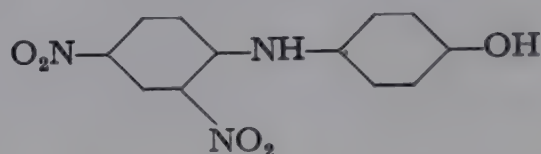
Of all the blue sulphur dyes, *IMMEDIAL PURE BLUE*, which is prepared by heating the indophenol $(\text{CH}_3)_2\text{N—}$  —N=  =O with alkali sulphides, first gave the clearest insight into the constitution of these dyes. Gnehm and Kauffler were able to show that a bromo-derivative of the previously partially desulphurized dye is identical with brominated Methyl violet (I). From this it follows that *Immedial pure blue* contains a thiazine ring. M. Schubert has established recently, that in the sulphurization of the indophenols the substituents in the benzene ring of the indophenol exert an influence on the properties of the dye formed. Substituents present in the quinonoid ring of the indophenol, however, are either split off, or they prevent the formation of a sulphur dye. Hence, it must be concluded that the sulphur enters the quinonoid nucleus and probably substitutes all the three available positions of the latter. Extensive investigations have shown that the sulphur fulfils a twofold function: In the positions 3 and 4 it effects the linking with a second thiazine molecule with the formation of a thi-anthrene nucleus, and in position 1 it forms disulphide bridges.

Immedial pure blue is thus to be considered as having formula II:

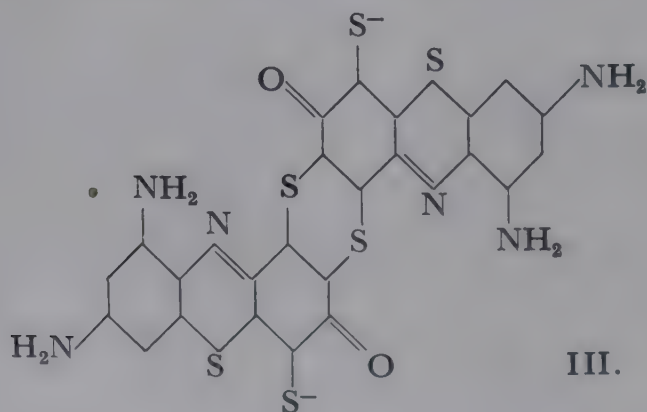


On reduction of the dye with sodium sulphide, the corresponding mercaptan would be produced, which is brought on to the fabric, and there re-oxidized by atmospheric oxygen to *Immedial pure blue*.

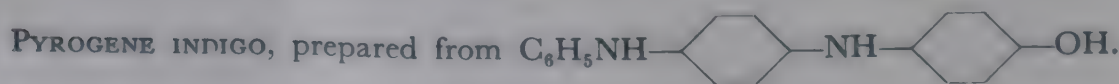
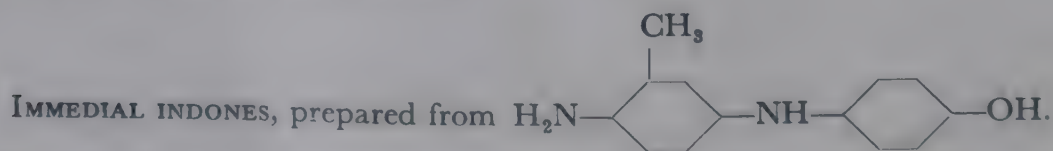
It has already been mentioned that, in particular, diphenylamine derivatives, indophenols, and their leuco-compounds provide starting materials for the preparation of blue and black sulphur dyes. The first great success in the field of the sulphur dyes was the preparation of **IMMEDIAL BLACK V EXTRA** from 2:4-dinitro-4'-hydroxydiphenylamine:



by fusion with sulphur. Bearing in mind what has been said above, the most probable formula for *Immedial black V extra* is the following (III):

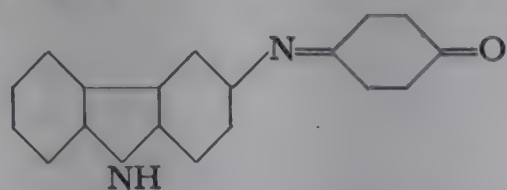


In addition to the above-mentioned *Immedial pure blue*, the following blue sulphur dyes must be mentioned:



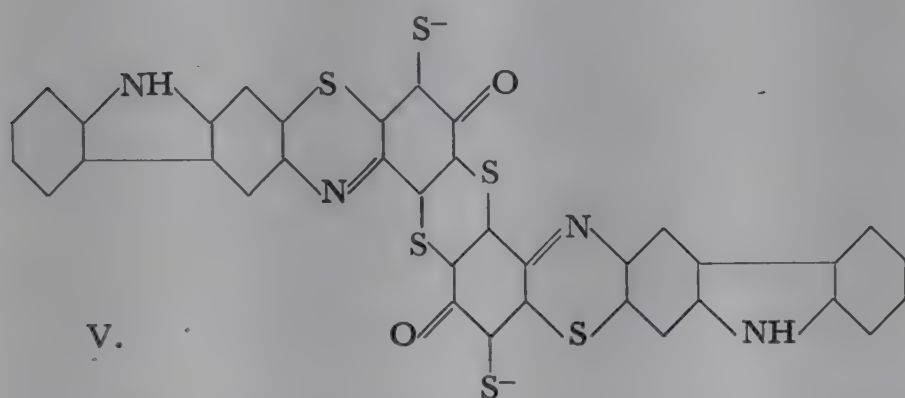
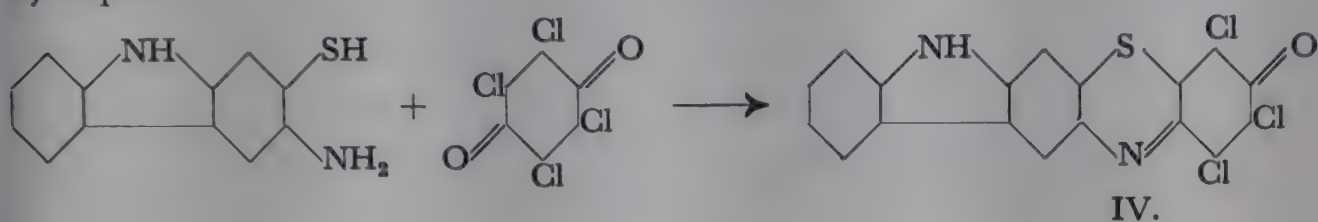
ECLIPSE BLUE, prepared from a dimethyl-*p*-amino-*p'*-hydroxy-diphenylamine-sulphonic acid.

HYDRON BLUE. This is at present the most important blue sulphur dye, and successfully competed with indigo. It is formed by boiling an alcoholic solution of an indophenol, which is prepared from carbazole and nitrosophenol:

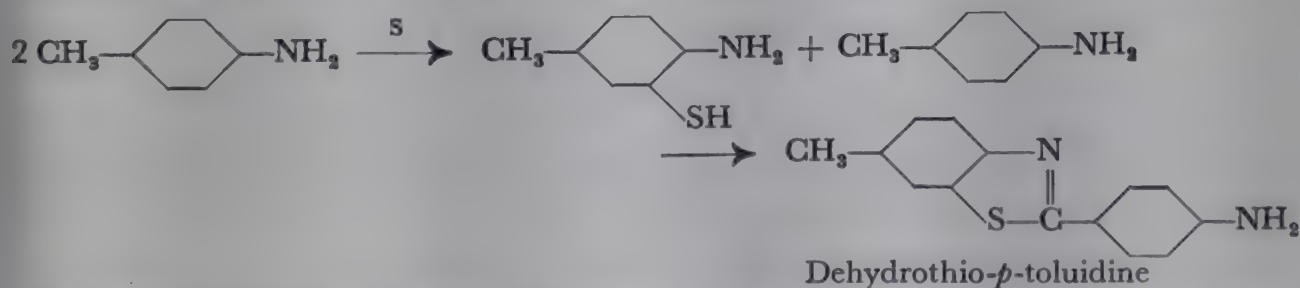


with sodium polysulphide (Na_2S_6). It is vatted not with sodium sulphide, but with sodium hydrosulphite, and dyes cotton blue, very fast to light and washing.

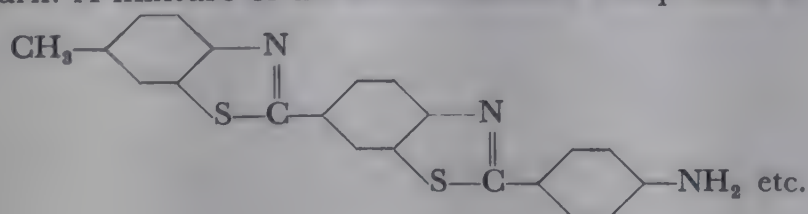
Its constitution can, in the main, be regarded as established. It is a thiazine dye substituted with disulphide groups (V). Hydron blue has been identified with a dye produced by converting 3-aminocarbazole into the *o*-mercaptan, condensing this with chloranil, and finally replacing the chlorine atoms in the violet condensation product (IV) by sulphur:



Yellow sulphur dyes. One of the oldest and best-known yellow sulphur dyes is PRIMULINE YELLOW (Green, 1887). If *p*-toluidine is heated with sulphur, a mercaptan is first formed, as in other cases, which then condenses with a second molecule of *p*-toluidine to form a thiazole compound, dehydrothio-*p*-toluidine:

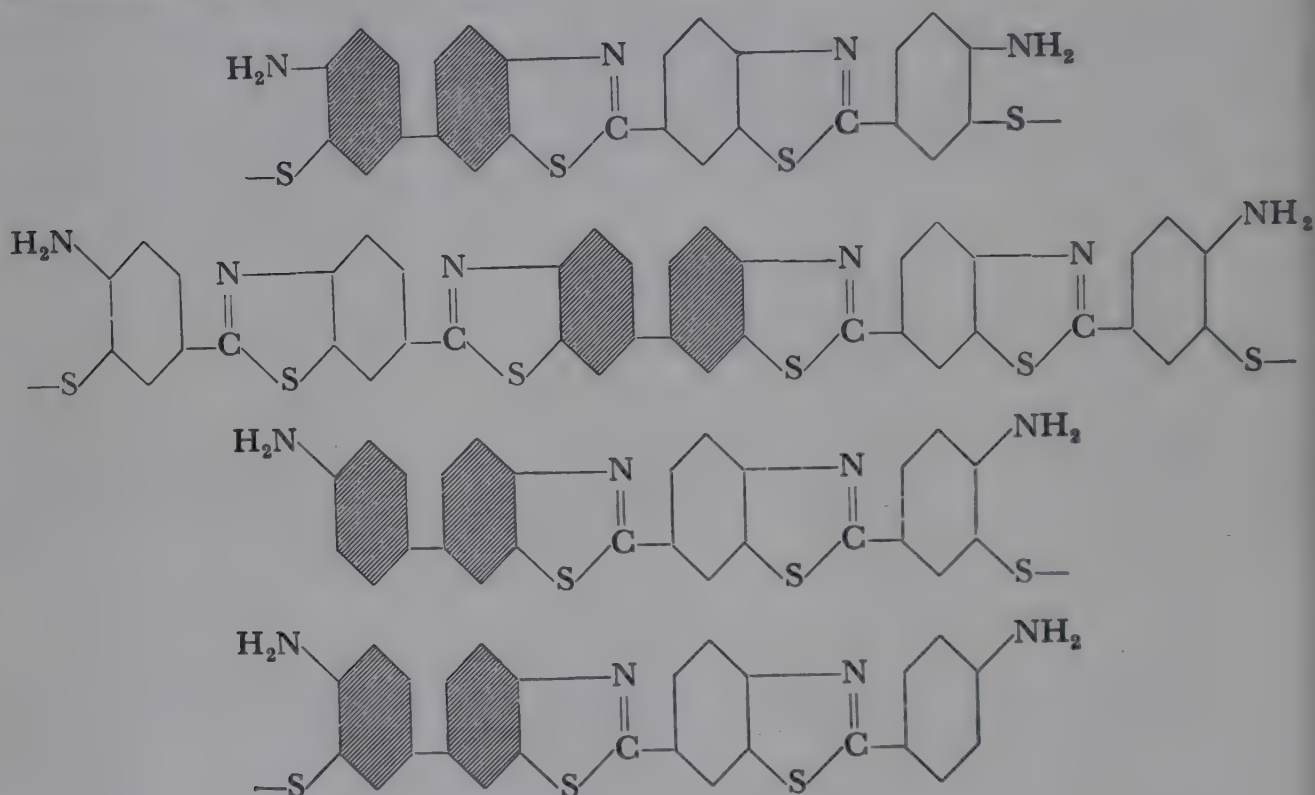


If the temperature of the fusion is raised to about 220° , the monothiazole-derivative condenses in turn. A mixture of di- and trithiazole compounds is produced:



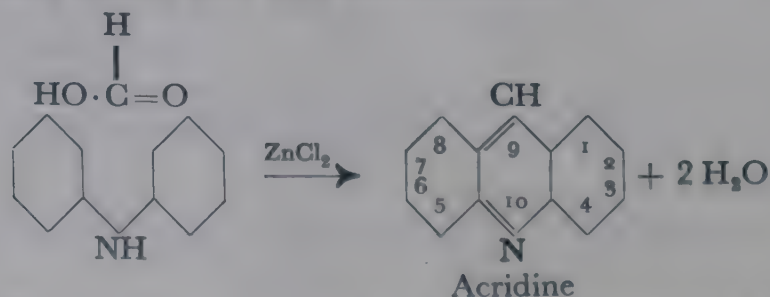
These very difficultly soluble, yellow substances are subsequently sulphonated. Sodium and ammonium salts of these sulphonated products come on to the market as *Primuline*. Primuline is not a very fast dye. It is, therefore, usually diazotized on the fibre and coupled with β -naphthol to give a red dye, fairly fast to washing. The diazo-compound of primuline is extremely sensitive to light, and has even found some use in photography in a copying process.

The Primuline base available commercially is not a homogeneous substance. M. Schubert has found recently that it contains, in addition to the above-mentioned di- and tri-thiazole compounds, mercapto-derivatives of these aminothiazole derivatives, in which the —SH -group stands in the *ortho*-position to the amino-group. Other yellow sulphur dyes ("Backfarbstoffe"), too, are such mercapto-compounds; e.g. IMMEDIAL YELLOW GG which is obtained by sulphurization of *p*-toluidine and benzidine. It is a mixture of 4 thiazole compounds, in which the benzidine radical is linked to the dehydrothiotoluidine through one or two thiazole rings. The solubility of the dye in sodium sulphide is due to disulphide groups standing in the *ortho*-position to the amino groups:



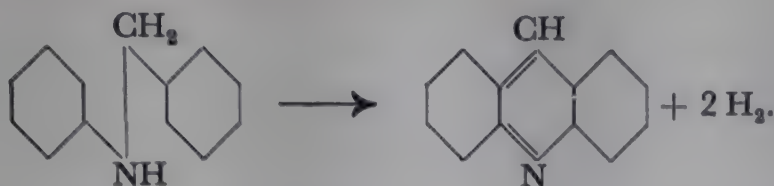
E. Acridine dyes¹

The parent substance of this group of dyes is *acridine*, which is contained in small amounts in coal-tar. It can be obtained synthetically, e.g. by heating diphenylamine with formic acid and zinc chloride:



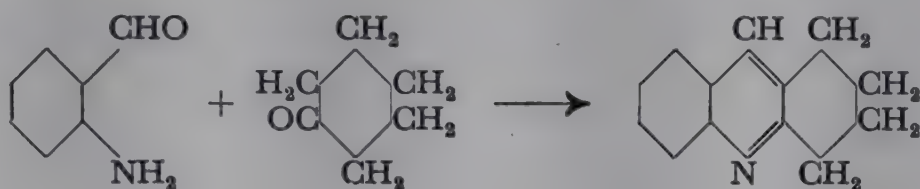
¹ See J. T. HEWITT, *Dyestuffs derived from Pyridine, Quinoline, Acridine and Xanthene*, London, (1922).

or from benzylaniline by passing it through a red-hot tube:

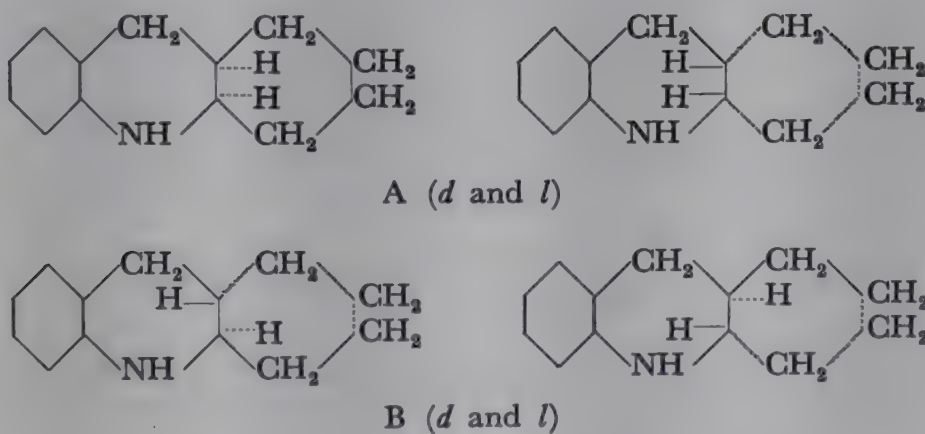


Acridine forms colourless needles, m.p. 108° . It has a characteristic smell, and shows a strong blue fluorescence in solution, which is characteristic of many acridine derivatives. With strong mineral acids it gives yellow, well-crystallized salts, which, however, are partially hydrolysed by the action of boiling water.

Strong oxidizing agents decompose acridine into quinoline- α,β -dicarboxylic acid (acridinic acid). Reducing agents (e.g. sodium amalgam) attack first the pyridine nucleus, giving 9:10-dihydroacridine. Acridine-1:2:3:4-tetrahydride has been obtained synthetically from *o*-aminobenzaldehyde and cyclohexanone:



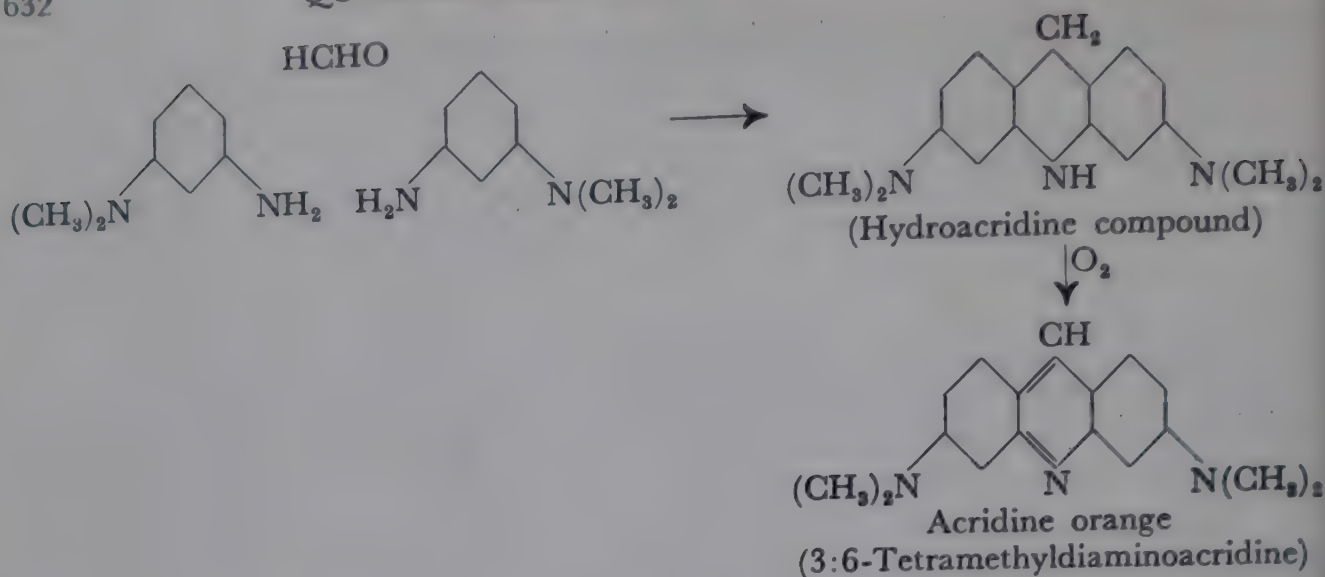
It has served for the preparation of the stereochemically interesting octahydroacridines. W. H. Perkin obtained two octahydroacridines, A and B, by the catalytic reduction of tetrahydroacridine. They could both be resolved into optically active forms. Hence, in one the hydrogenated benzene ring must be attached in the *cis*-position, and in the other in the *trans*-position, to the hydrogenated pyridine ring of the octahydroacridine:



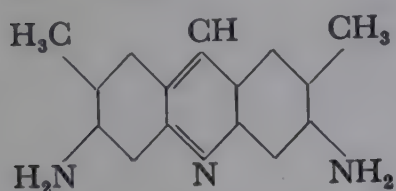
The isomerism encountered here is analogous to that of the two decahydro- β -naphthols (see p. 408).

A number of dyes is derived from acridine, which, however, are not prepared from the rather difficultly obtainable parent substance acridine itself, but by other methods. The following deserve mention:

ACRIDINE ORANGE NO. This is synthesized from *as*-dimethyl-*m*-phenylenediamine and formaldehyde, which condense on heating to give the hydroacridine derivative. Atmospheric oxygen oxidizes this to the dye:

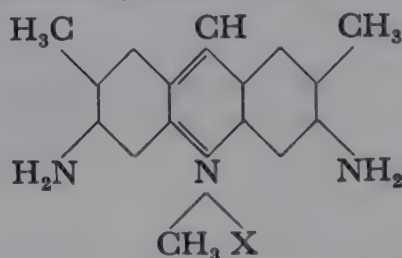


Acridine orange occurs in commerce as the zinc chloride double salt. It gives a fluorescent colour on tanned cotton and silk which is fairly fast to washing but not very fast to light.

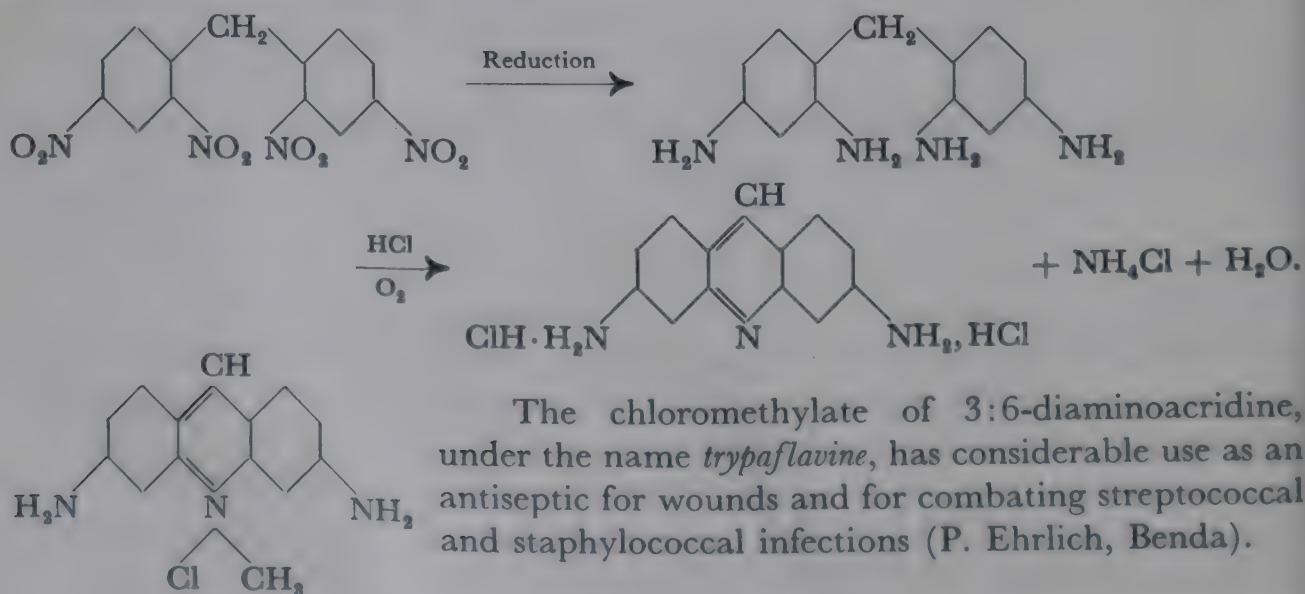


ACRIDINE YELLOW is made in a similar way to the above-mentioned compound from *m*-toluylendiamine and formaldehyde. It resembles Acridine orange also as regards dyeing properties.

In order to increase the solubility of the acridine dyes, they are often converted into acridinium compounds by alkylation at the ring nitrogen atom 10. In this way, for example, Acridinium yellow is obtained from Acridine yellow:

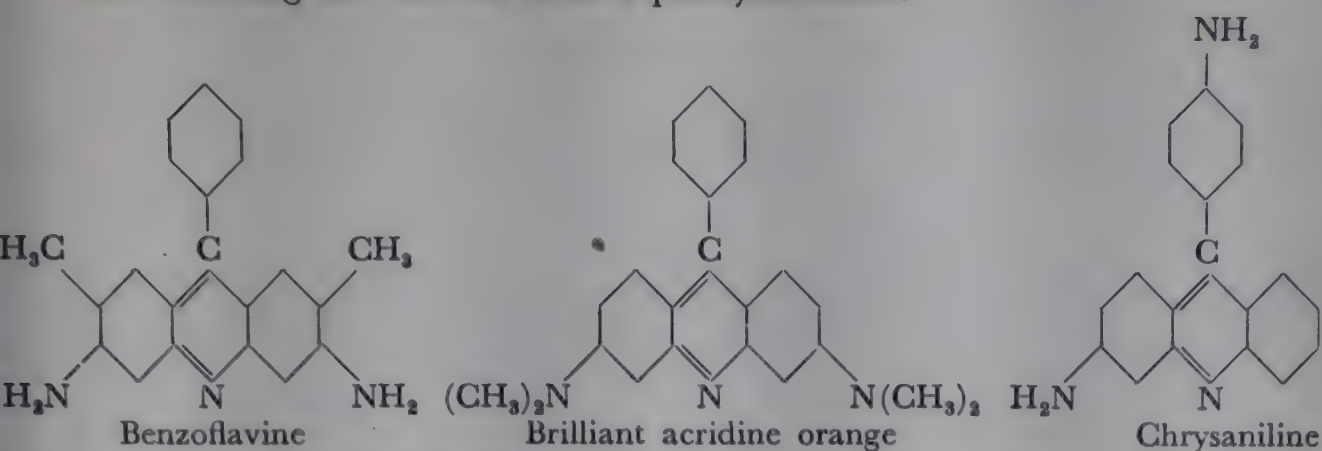


TRYPAFLAVINE. 3:6-Diaminoacridine cannot be obtained from formaldehyde and *m*-phenylenediamine. It is necessary to start with bis-(dinitrophenyl)-methane, which is reduced to the tetraamino-compound, and this is converted into 3:6-diaminoacridine through the hydroacridine derivative by heating with hydrochloric acid in autoclaves:



The chloromethylate of 3:6-diaminoacridine, under the name *trypaflavine*, has considerable use as an antiseptic for wounds and for combating streptococcal and staphylococcal infections (P. Ehrlich, Benda).

The following are derived from 9-phenylacridine:

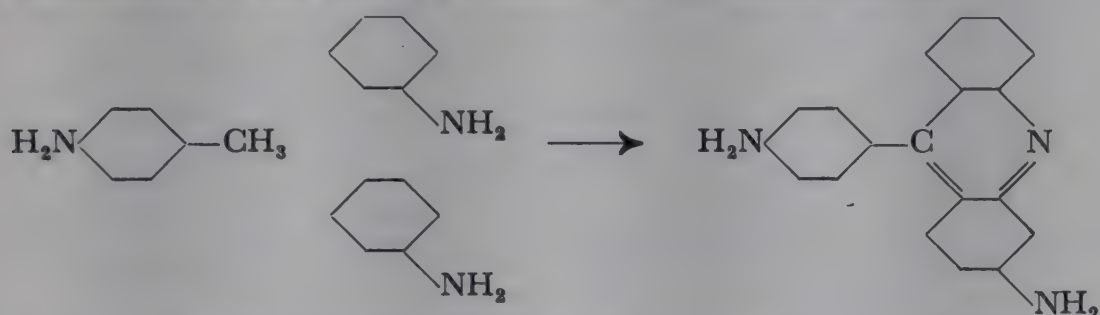


BENZOFLAVINE is made from benzaldehyde and *m*-toluylenediamine.

It dyes tanned as well as unmordanted cotton yellow, and is used particularly in calico printing.

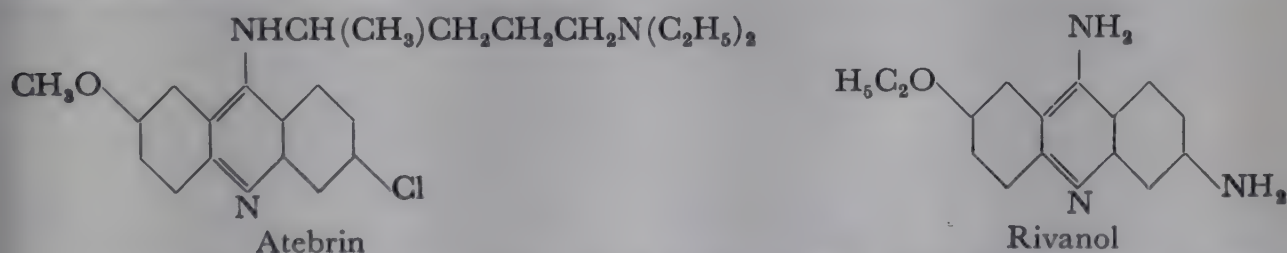
BRILLIANT ACRIDINE ORANGE is obtained in a similar way (from *as*-dimethyl-*m*-phenylenediamine).

CHRYSANILINE is a by-product in the manufacture of fuchsin, where it is produced by the condensation of one mol. of *p*-toluidine with 2 mols. of aniline:



A mixture of salts (chlorides or nitrates) of chrysaniline and homologues, which is isolated from the residues from the fuchsin fusion, occurs in commerce under the name "*Phosphine*" and others. It dyes unmordanted and tanned cotton brown-yellow, but is chiefly used in the dyeing of leather.

Certain derivatives of 9-aminoacridine are of chemo-therapeutic interest.¹ *Atebrin* and *Rivanol* are compounds the first of which is recommended for the treatment of malaria, and the second for amœbic dysentery:

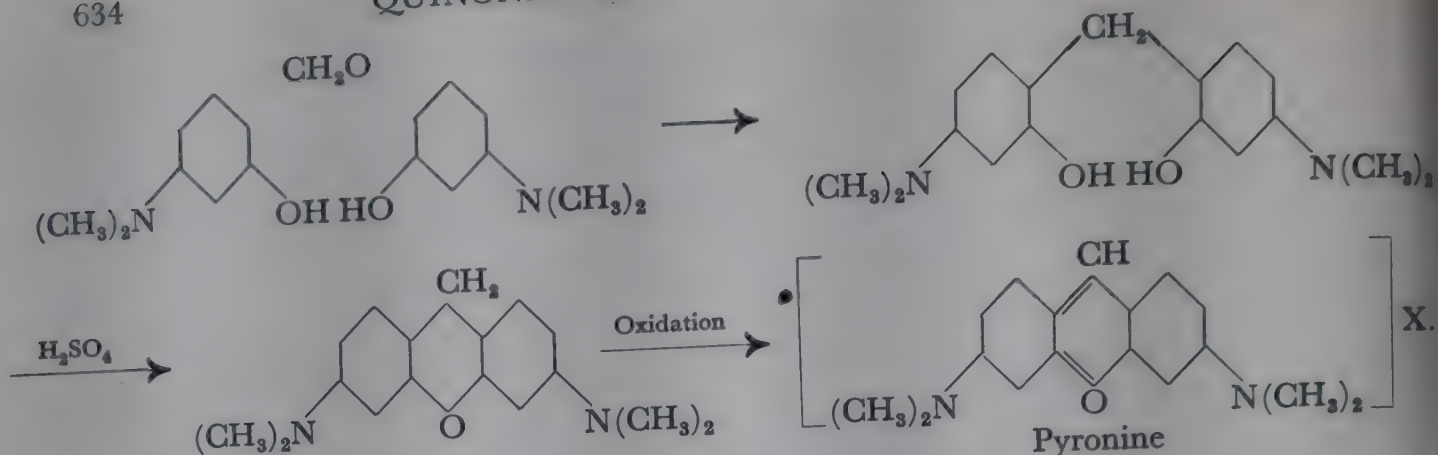


Atebrin (mepacrine) has been resolved into optically active forms ($[\alpha]_D = \pm 195^\circ$). Atebrin isolated from human urine is the *l*-form.

F. Xanthylum salts

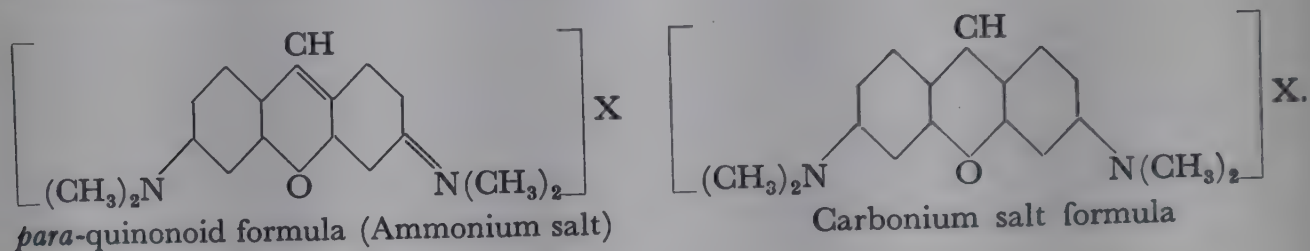
(a) **Pyronines**. These are formed by condensation of *m*-dimethylamino-phenol or its homologues with formaldehyde. Tetramethyldiamino-dihydroxy-diphenylmethane is formed as an intermediate product. It loses water with sulphuric acid to give the cyclic ether (leucopyronine), and the latter is then oxidized to give the dye:

¹ See V. FISCHL and H. SCHLOSZBERGER, *Handbuch der Chemotherapie*, I. Teil: *Metallfreie organische Verbindungen*, Leipzig, (1932).



Pyronine dyes silk and wool red with a yellow fluorescence, and will also dye tanned cotton. It is not very fast to light.

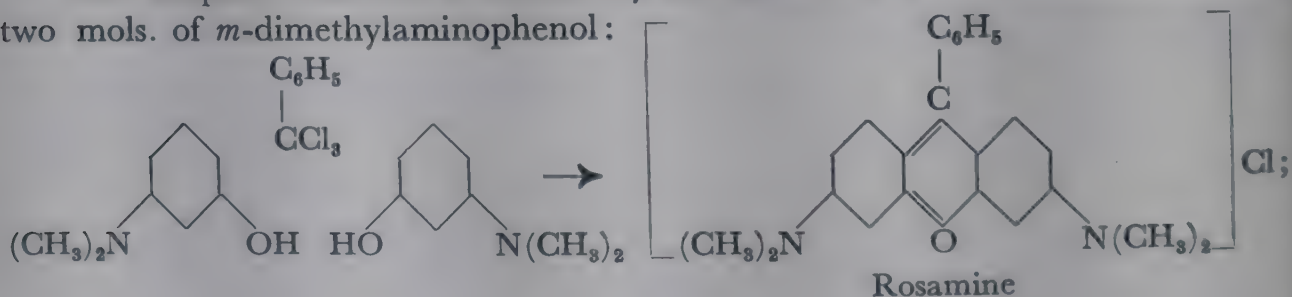
In addition to the above *ortho*-quinonoid (oxonium salt) formulation, pyronine may also be written as a *para*-quinonoid (ammonium salt) compound, and further as a carbonium salt. This holds similarly for the rosamine, rhodamine, and fluorescein dyes considered below.



As in the case of the triphenylmethane dyes there is at present no possibility of deciding definitely between these formulations.

(b) **Rosamines** are phenylated pyronines. They dye silk, but are practically no longer used, as their quality does not come up to that of the similarly constituted rhodamines described below.

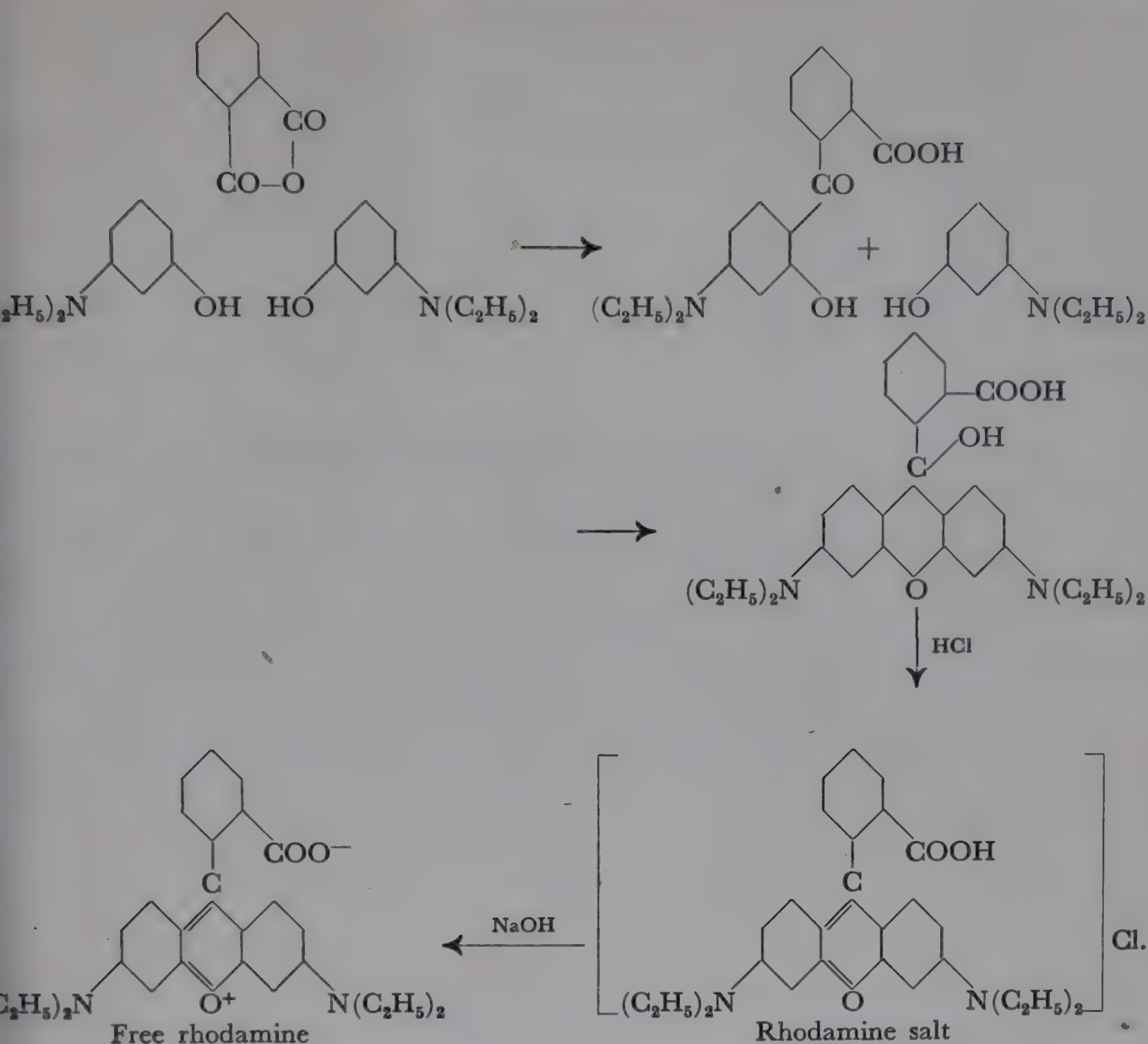
The simplest rosamine is formed by condensation of benzotrichloride with two mols. of *m*-dimethylaminophenol:



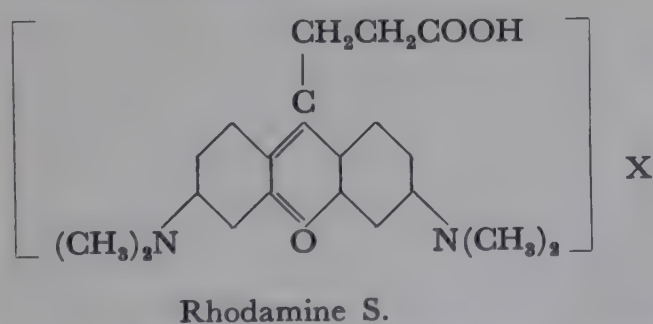
Alkalis convert rosamine first into the dye-base, and then into the colourless carbinol-base, from which mineral acids regenerate the dye.

(c) **Rhodamines** likewise belong to the pyronine derivatives and are obtained by the condensation of phthalic anhydride or succinic anhydride with *m*-aminophenols. They contain a carboxyl group, and therefore possess acidic as well as basic properties.

The first rhodamine to be prepared was Rhodamine B, which was made by Cérésol from phthalic anhydride and *m*-diethylaminophenol:



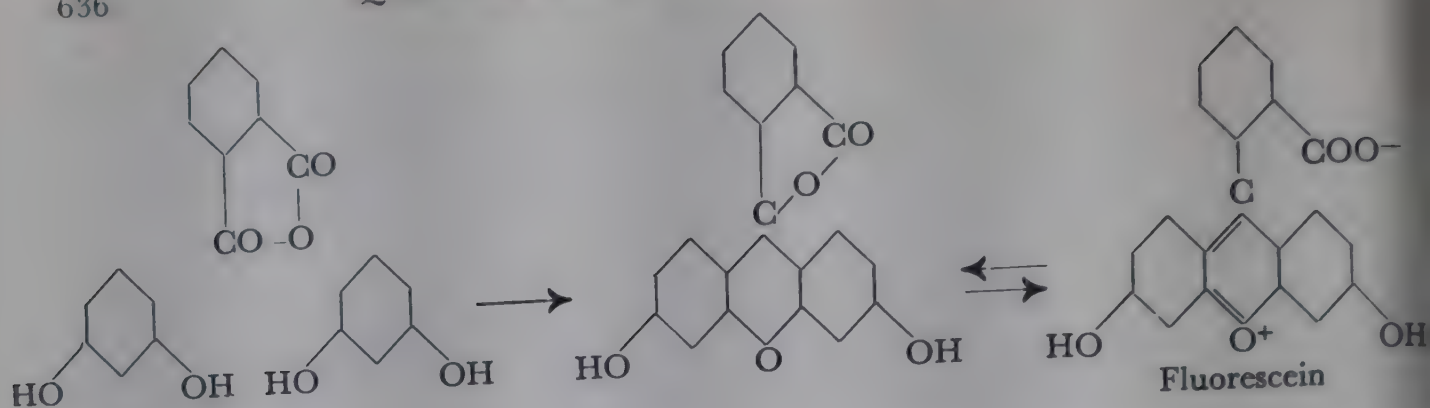
Another dye belonging to this group is *Rhodamine S*, prepared from succinic anhydride and *m*-dimethylaminophenol:



The rhodamines dye silk and wool, and in part, cotton a bluish red with a strong fluorescence. No fluorescence is observed on tanned cotton. The colours are not very fast to light.

Esters of the rhodamine salts can also be prepared. They are substantive cotton dyes.

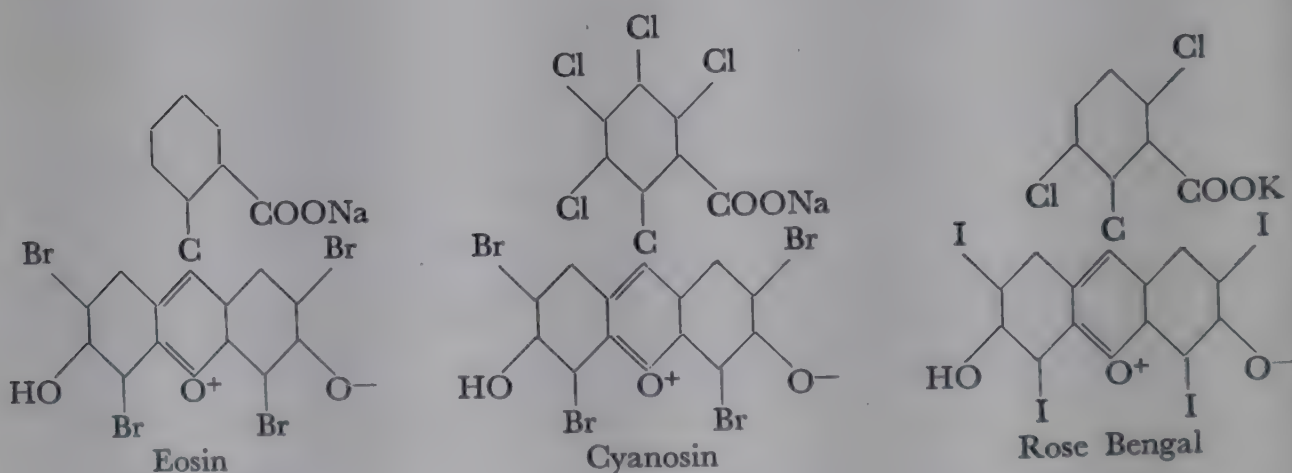
(d) Fluoresceins. The fluoresceins are distinguished constitutionally from the rhodamines in that they contain hydroxyl groups in place of the amino-groups. They are made from phthalic anhydride and *m*-dihydroxybenzenes (resorcinol, pyrogallol) by fusing them together:



Fluorescein forms dark yellow crystals, which dissolve in alkalis to give an orange solution with a strong, splendid green fluorescence. This is so intense that it allows the detection of traces of the substance. The fluorescein test serves for the qualitative detection of *m*-dihydroxybenzenes on the one hand, and on the other of phthalic anhydride. An interesting use of the dye is in the determination of the communications between different waters.

As a dye, fluorescein has no importance on account of its insufficient fastness. It serves, however, as a starting material for the preparation of most eosins.

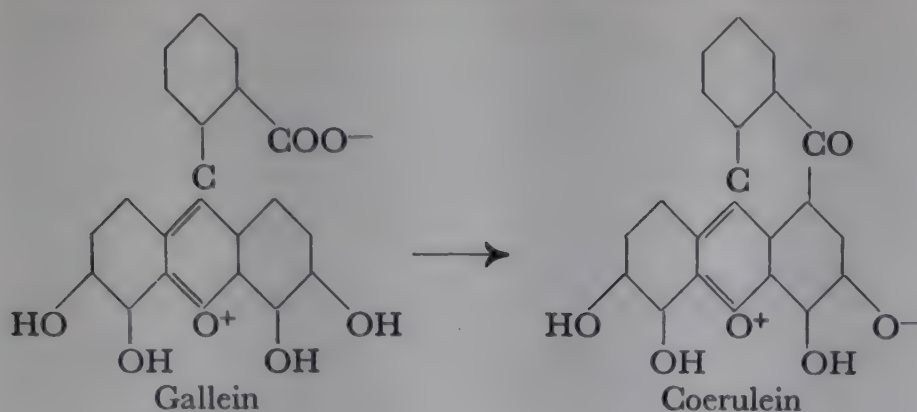
Ordinary EOSIN is the sodium salt of tetrabromofluorescein. It dyes silk and wool a brilliant red:



The corresponding iodo-derivative is known as *Erythrosin*. Esters of fluorescein are also used in dyeing, such as the sodium salt of tetrabromofluorescein ethyl ester, which, on account of its solubility in alcohol, is known as *Spirit eosin*.

If resorcinol is fused with dichloro- or tetrachlorophthalic anhydride, instead of with phthalic anhydride itself, and the fluoresceins so obtained are brominated or iodinated, dyes such as *Cyanosin* (phloxin) and *Rose Bengal* are produced. They are used in dyeing silk, paper, varnishes, and tin-foil, etc.

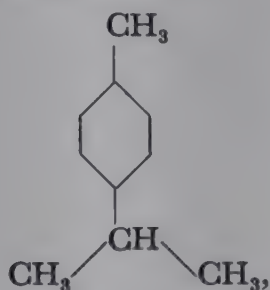
The condensation of pyrogallol or gallic acid with phthalic anhydride gives *Gallein*. It is red. Its alkali salts are blue, and the aluminium and chrome lakes violet. By the action of concentrated sulphuric acid, gallein is converted, by adding a new ring system, into *Coerulein*, a derivative of anthraquinone. The chrome lake of this dye is valued for silk, wool, and cotton dyeing, and in calico printing, on account of its excellent fastness:



B. Alicyclic Compounds¹

CHAPTER 50. INTRODUCTION

Carbocyclic compounds which are aliphatic in character belong to the group of alicyclic compounds. The group therefore comprises the polymethylenes and their derivatives, the *cyclopropane*, *cyclobutane*, *cyclopentane*, *cyclohexane* compounds, and higher ring homologues. The *saturated* alicyclic hydrocarbons are also commonly called *naphthenes*. *Unsaturated* hydrocarbons of the *cyclohexane* series, particularly those derived from *p*-cymenē:



are called *terpenes*, and their oxygen-containing derivatives are sometimes called *camphors*.

Natural occurrence of naphthenes, terpenes, and camphors. Naphthenes form a considerable proportion of the Galician and Caucasian mineral oils (see p. 39) and of many asphalt oils. Most American petroleum, on the other hand, contain only very small quantities of naphthenes. In spite of the enormous quantities of naphthenes which occur in Russian mineral oil, this is only rarely used for the preparation of *pure* naphthenes, since the separation of such mixtures of hydrocarbons into individual substances presents considerable difficulty.

¹ See OSSIAN ASCHAN, *Chemie der alicyclischen Verbindungen*, Brunswick, (1905). — O. WALLACH, *Terpene und Campher*, Berlin, (1914). — FR. WILH. SEMMLER, *Die ätherischen Öle*, Bd. 1-4, Berlin, (1906-07). — F. G. POPE, *Modern Research in Organic Chemistry*, New York, (1912), Chs. I and II, *The Polymethylenes; The Terpenes and Camphors*. — B. T. BROOKS, *The Chemistry of the Non-Benzenoid Hydrocarbons*, New York, (1922). — J. L. SIMONSEN, *The Terpenes*, Cambridge, (1932). — OSSIAN ASCHAN, *Naphtenverbindungen, Terpene und Campherarten inkl. Pinusharzsäuren sowie Körper der Kautschukgruppe. Eigene Beiträge zur Chemie alicyclischer Verbindungen*, Berlin, (1929). — ALFRED WAGNER, *Die Riechstoffe und ihre Derivate*, Vienna, (1929). — J. W. BAKER, *Natural Terpenes*, London, (1930). — E. GILDEMEISTER and F. HOFFMANN, translated by E. Kremers, *The Volatile Oils*, London, (1940). — ERNEST GUENTHER, *The Essential Oils*, New York (1948).

Terpenes and camphors are found in *essential oils*, readily volatile substances from the flowers, leaves, fruits, or roots, and occasionally also from other parts of many plants. The majority of essential oils are complex mixtures of many, often similarly constituted, substances. Their composition undergoes variation, and is dependent upon the place where the plant grows, the climatic conditions, and the time of year.

The extraction of essential oils is an important industry in many countries, particularly those in Southern Europe (France, Italy, the Balkans, Turkey, etc.). The method of extraction varies from plant to plant and often from one part of the country to another.

A simple process is that of *expressing* the essential oil, which, for example, is used in the case of preparing oils from lemon, orange, and bergamot peel in Sicily, and is carried out by hand.

Other essential oils are separated by *steam distillation*. Thus lavender flower oil is obtained in this way in the South of France, and rose oil in Bulgaria. The amount of the latter produced is sometimes as much as 5,000 kg per annum. Since 2,000 to 3,000 kg of roses are required to produce 1 kg of rose oil, one can imagine the number of flowers needed to prepare this amount.

Other essential oils are isolated from the plants by *extraction* with ligroin, chloroform, ether, alcohol, etc. The yields are often not very large, but the oils are pure, and therefore valuable. A special method of extraction uses as the extracting agent hot (70°) fat, generally consisting of a mixture of 30% purified beef fat and 70% purified lard. The solution of the oil in fat obtained by this "*maceration process*", comes on to the market as "flower pomade".

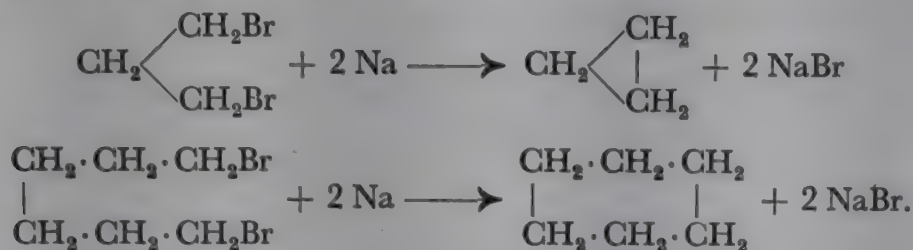
In the modern "*enfleurage method*" developed in the South of France, the essential oils of the flower petals are extracted by solid fat at ordinary temperatures. Glass plates, fixed in wooden frames, the so-called chassis, are covered with a layer of fat, a large number of such chassis being arranged one above the other. The petals are scattered between the fat-covered glass plates, which are about 5 cm apart. The essential oils slowly pass into the fat. When the petals become exhausted, they are replaced by new ones, and the process is repeated until the fat becomes saturated with the oil. The "*enfleurage*" method furnishes in some cases (as with jasmine, and tuberoses) considerably higher yields of essential oils than the other methods. This depends on the fact that the petals, during their several days' stay in the chassis, form new oil. They thus continue to live. For jasmine, for example, the yield can amount to ten times that obtained by the extraction method.

Some perfumes are not contained in the free form in plants, but as derivatives, e.g. glycosides. To hydrolyse them the parts of the plant concerned are allowed to stand in water. The enzymes present in the plant then effect the hydrolysis. In this way benzaldehyde is formed from amygdalin (q.v.), and allyl mustard oil from sinigrin, a glycoside present in mustard seed.

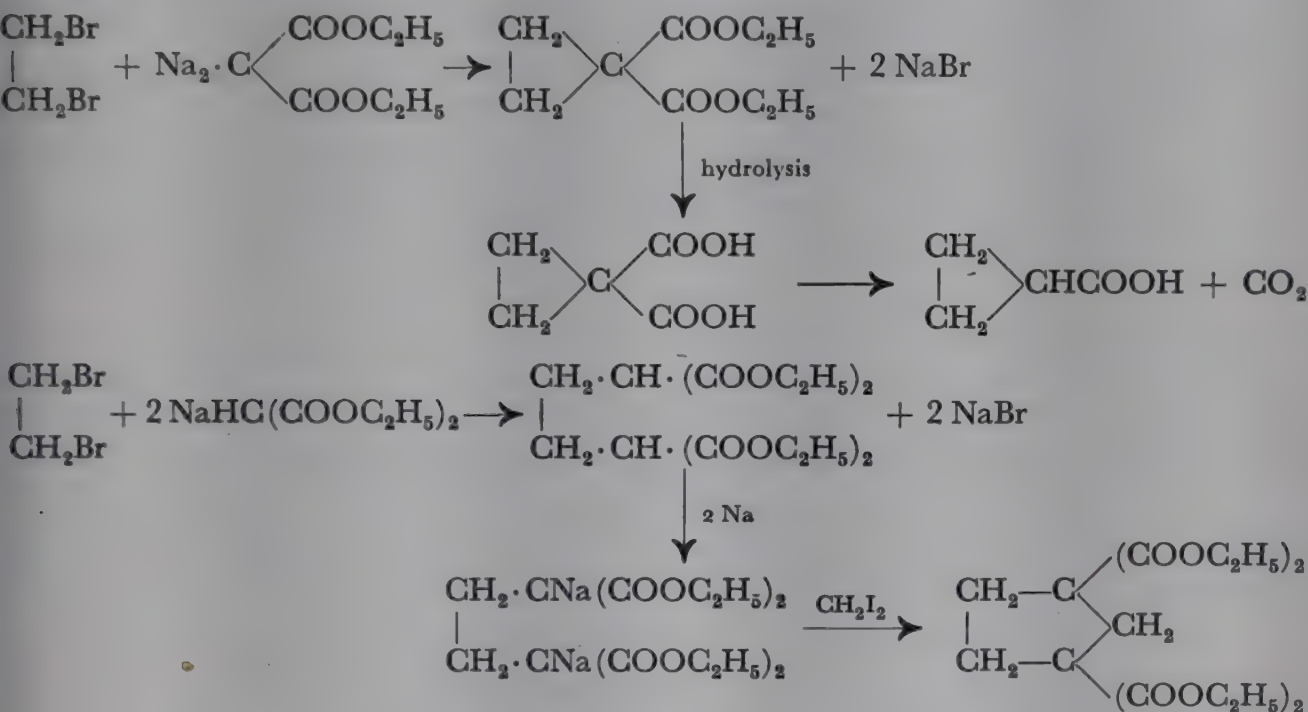
Syntheses of alicyclic compounds. A large number of methods, which, in part, are based on those used in the aliphatic series, are available for the synthesis of alicyclic compounds. These reactions proceed particularly smoothly, and with good yields, when they lead to the stable five- and six-membered ring

systems (see p. 245, Baeyer's strain theory), but the chemistry of *cyclopropane* and *cyclobutane* is also well developed.

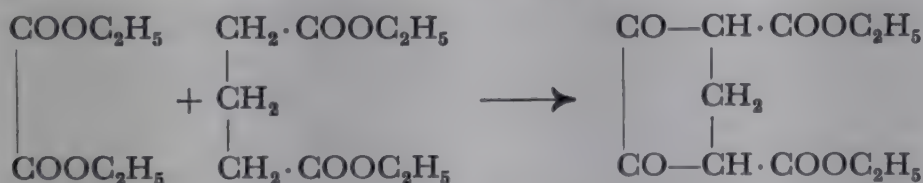
1. Alicyclic compounds may be obtained by the action of sodium on dihalogen compounds which do not contain vicinal halogen atoms:



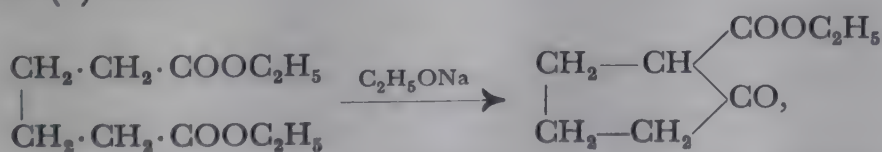
2. Alicyclic carboxylic acids can be synthesized from disodiomalonic ester and from monosodiomalonic ester, e.g.:



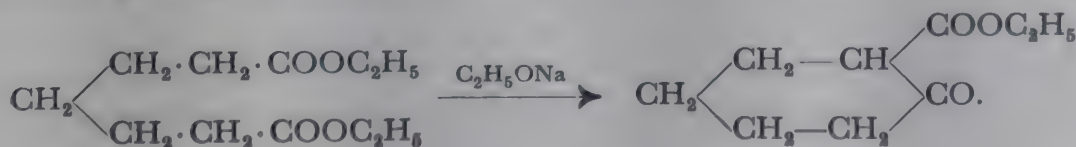
3. Esters of dicarboxylic acids can often be condensed by means of sodium ethylate to cyclic ketones by an extramolecular or intramolecular Claisen condensation (p. 267) (Dieckmann and Komppa's synthesis):



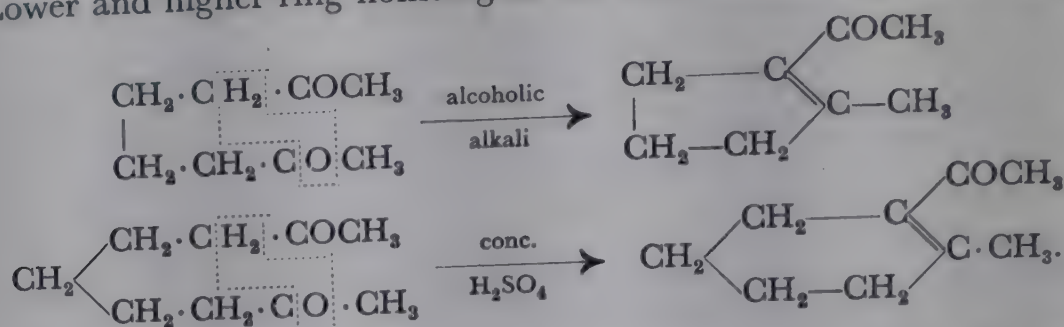
Adipic ester is converted by means of sodium ethylate into *cyclopentanone*-(2)-carboxylic-(1) ester:



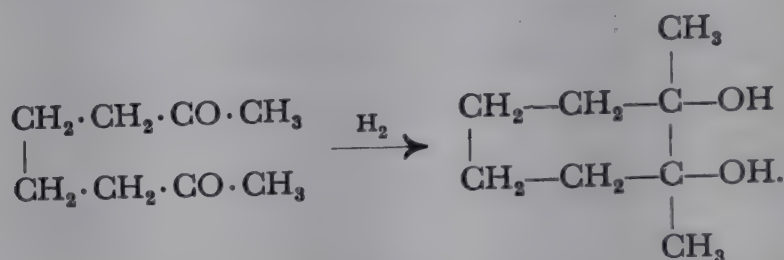
Pimelic ester gives *cyclohexanone*-(2)-carboxylic-(1) ester in a corresponding way:



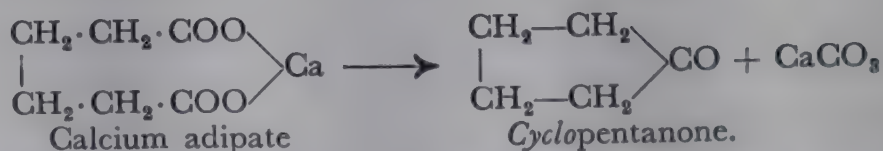
4. Certain diketones may be converted into unsaturated cyclic derivatives by intramolecular elimination of water. Ring closure only occurs, however, with those diketones (1:4, 1:5, 1:6-, and 1:7-) in which the relative positions of the two carbonyl groups makes possible the formation of the stable five- or six-membered rings. Lower and higher ring homologues are not obtained by this method:



5. The pinacol reduction, applied to diketones, may give rise to cyclic glycols:

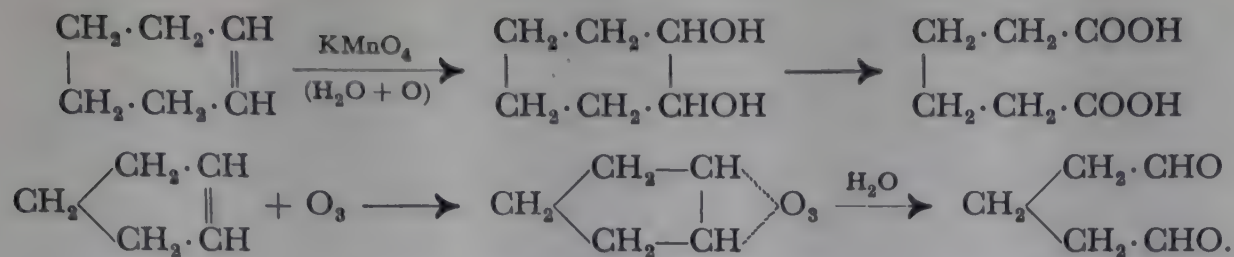


6. An important synthesis of cyclic ketones depends on the dry distillation of the calcium salts of dicarboxylic acids. The reaction occurs particularly smoothly with the calcium salts of adipic and pimelic acids, from which the very stable monoketones of *cyclopentane* and *cyclohexane* are obtained. Yet higher cyclic ketones can also be obtained by this method, though in poorer yield (see Ch. 57 and 58):



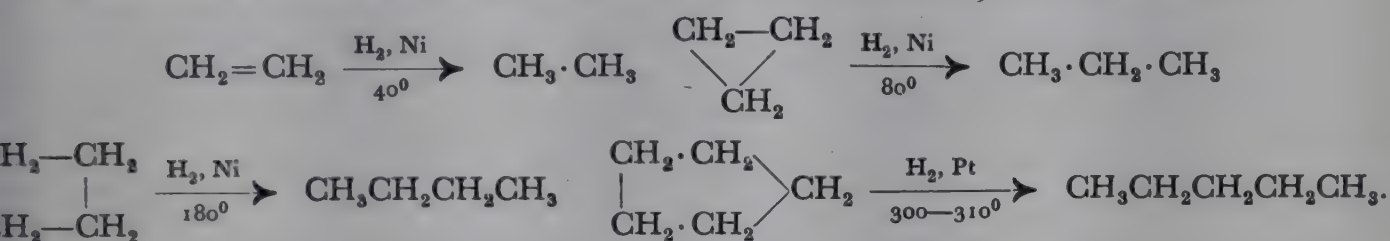
In certain cases it is more suitable to use other metal salts of the dicarboxylic acids instead of the calcium salts for this ring closure. Thus, Komppa found the *lead salt* of homo-apocamphoric acid specially suitable for preparing the cyclic ketone corresponding to this compound. Sabatier obtained good results in the conversion of dicarboxylic acids into cyclic ketones using manganese oxide as a catalyst. J. Vogel converted suberic acid into suberone by heating it with iron filings and powdered barium hydroxide, and according to Ruzicka, the thorium salts are the most suitable by far for converting the higher dicarboxylic acids into cyclic ketones (see also Ch. 58).

Ring-fission of alicyclic compounds. 1. Cyclic *unsaturated* hydrocarbons and their derivatives can readily be broken down at the unsaturated linkages by oxidation. Potassium permanganate (Wagner) and ozone (Harries) are suitable reagents. The reactions take a course exactly analogous to that in the ethylenic series, i.e. cleavage with potassium permanganate leading via glycols, which can be isolated (usually *cis*-diols, J. Böeseken), to dicarboxylic acids, and that with ozone giving dialdehydes, aldehyde-ketones, diketones, etc., through the ozonides:

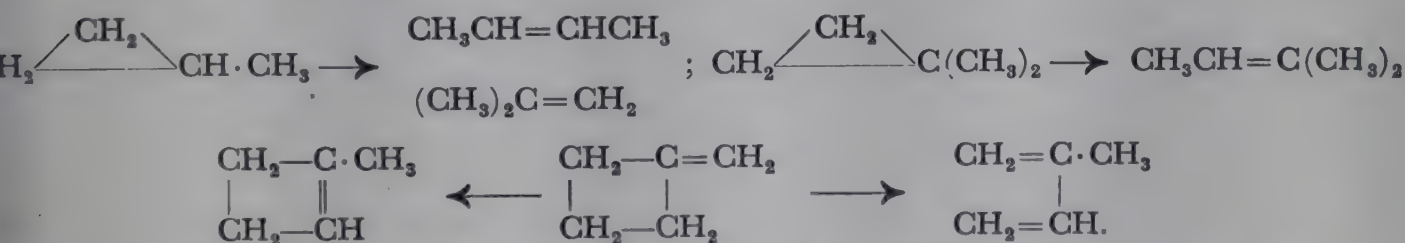


These methods of rupturing the rings are of considerable importance in determining the constitution of cyclic unsaturated compounds, since they proceed very smoothly.

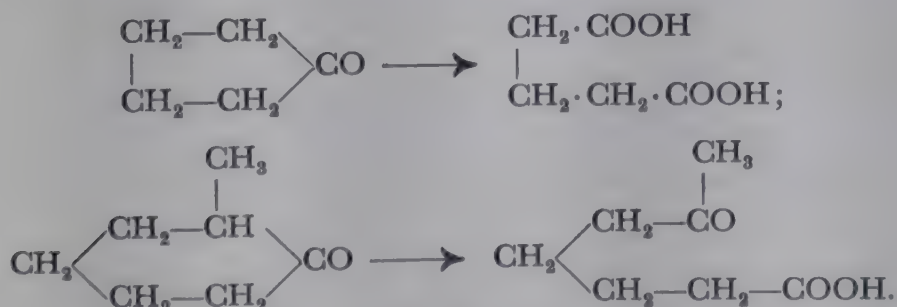
2. *Cyclopropane* and *cyclobutane* may be converted into paraffin hydrocarbons by hydrogenation, on being mixed with hydrogen and passed over heated nickel powder (Willstätter). For *cyclopropane* the reaction begins already at about 80° , and proceeds rapidly at 120° . The opening of the *cyclobutane* ring to give butane by hydrogenation requires a higher temperature, 180° , and the polymethylene rings in *cyclopentane*, *cyclohexane*, and *cyclooctane* are even more stable (e.g. *cyclopentane* requires a temperature of $300\text{--}310^\circ$ before the five-membered ring is broken by hydrogenation (Zelinsky)). When it is remembered that ethylene is hydrogenated by hydrogen and nickel at 40° , a connection between the stability of these ring systems and the ease with which they are broken is easily recognized:



3. If *cyclopropane* or *cyclobutane* compounds are passed over heated alumina, isomerization often occurs to olefins (Ipatieff, Dojarenko, etc.). As examples, the following may be given:

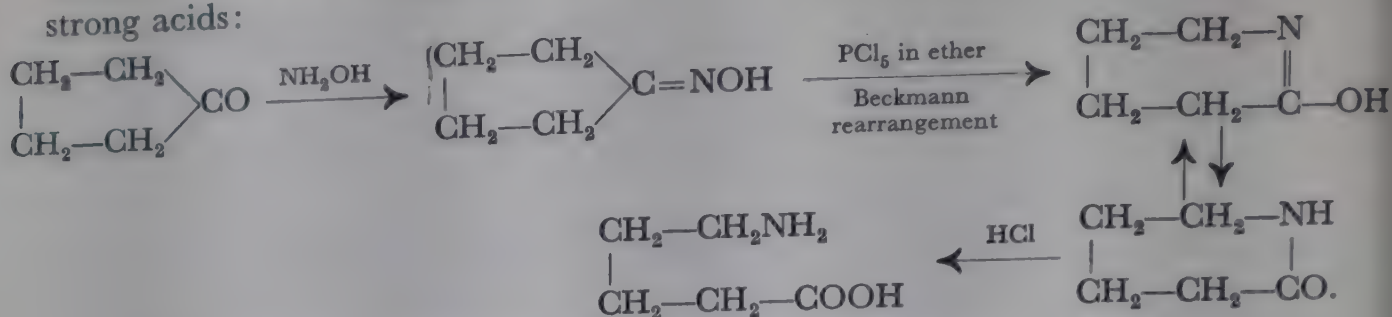


4. The ring in cyclic ketones can usually be readily opened by oxidation with nitric acid. The reaction products are dicarboxylic acids or keto- and hydroxy-acids:



Wallach has described a method whereby cyclic ketones can be converted into aliphatic amino-acids through the ketoximes. Like other oximes, also those of cyclic ketones undergo the Beckmann rearrangement, under suitable conditions.

The products are lactams, of which the ring may be opened by boiling with strong acids:



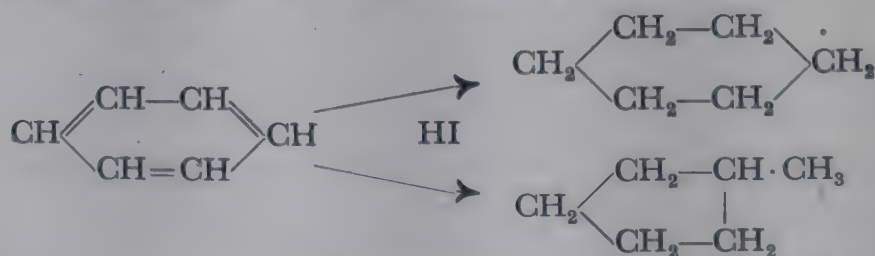
Conversion of one ring system into another. In the study of the reactions of alicyclic compounds one is often struck by the surprising phenomenon that apparently slight chemical action may result either in ring contraction or ring expansion. This does not take place merely with the more unstable *cyclopropane* and *cyclobutane* rings, but conversion even of *cyclopentane* derivatives into *cyclobutane* compounds is also encountered.

The recent discovery of Nenitzescu, that if *cyclohexane* and methyl*cyclopentane* are boiled with hydrated aluminium chloride, an equilibrium is reached between the two substances, is of great theoretical interest. This appears to be the first example of dynamic isomerism between hydrocarbons.

The mechanism of most of these reactions is at present still completely unknown. In a few cases only, may it be assumed that unstable intermediate products (e.g. bicyclic compounds) are formed, whose further decomposition gives rise to a lower or higher ring system different from that of the original substance.

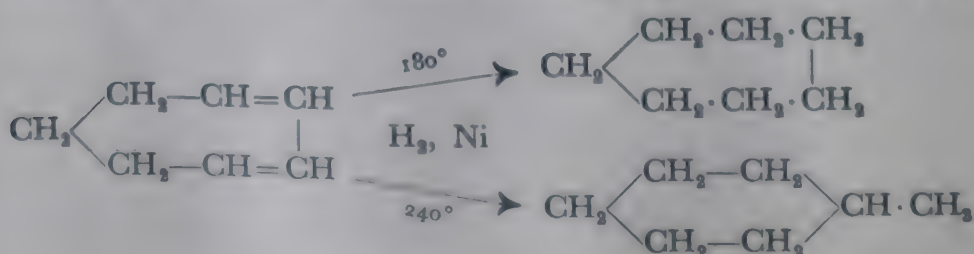
(a) METHODS OF RING CONTRACTION

1. On heating benzene or its homologues with hydriodic acid to 200–300° there are always formed, according to Zelinsky, difficultly separable mixtures of normal reduction products and those with smaller rings. Thus *cyclohexane*, methyl*cyclopentane* and *n*-hexane are chiefly obtained from benzene:

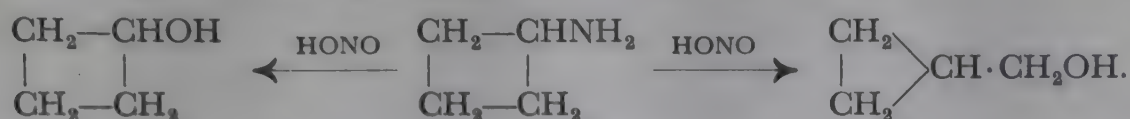


By the same treatment *cyclohexane* is partially isomerized to methyl*cyclopentane*. *Cycloheptane* gives methyl*cyclohexane* and dimethyl*cyclopentane* on heating with hydriodic acid.

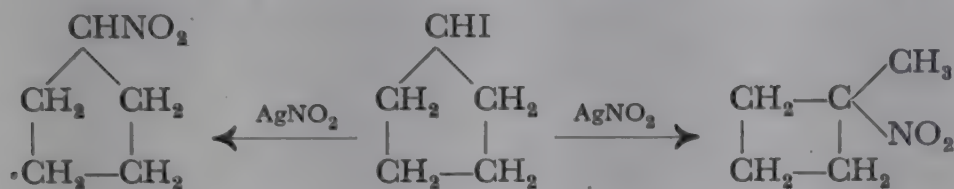
Cycloheptadiene, which is reduced in the normal manner to *cycloheptane* by means of hydrogen and a nickel catalyst at 180°, is converted at higher temperatures (230–240°) by means of the same reducing agent into methyl*cyclohexane*:



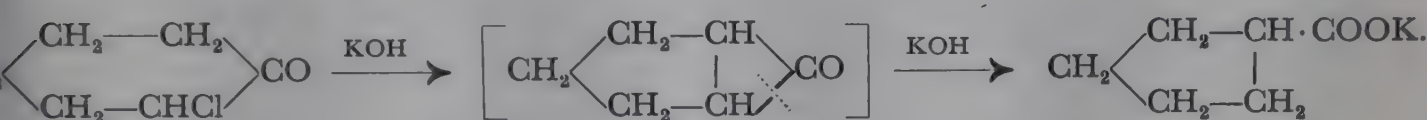
2. *Cyclobutylamine* is only partially converted into *cyclobutanol*, on treatment with nitrous acid, for at the same time there is a contraction of the ring and considerable quantities of *cyclopropylcarbinol* are formed:



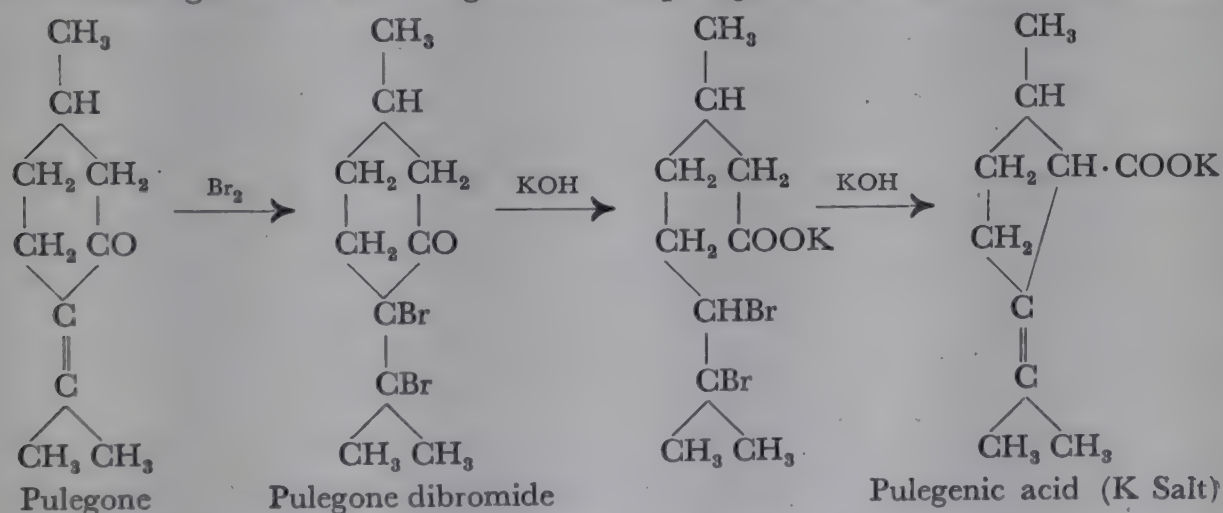
3. *Iodocyclopentane* and silver nitrite likewise react in two ways. In addition to the nitro-compound of *cyclopentane*, one of *methylcyclobutane* is also produced:



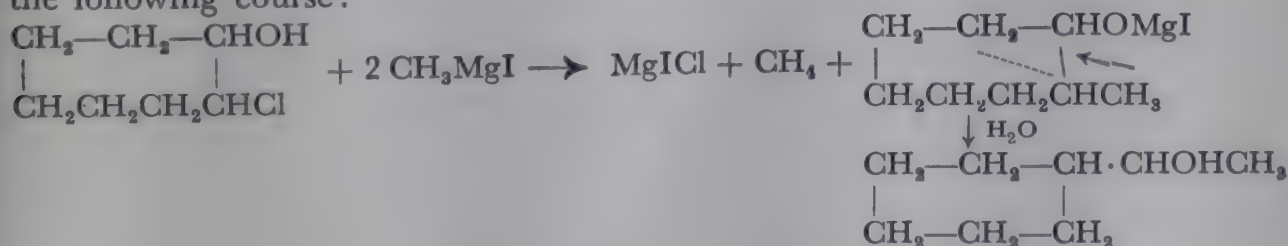
4. The action of caustic alkalis on cyclic α -chloroketones is often accompanied by a contraction of the ring. Bicyclic compounds containing a trimethylene ring appear to be formed as intermediate products. In the second stage of the reaction, their *cyclopropane* ring is hydrolytically opened, the monocyclic *cyclopentane* derivative being formed, e.g.:



An analogous case is the degradation of *pulegone* to *pulegenic acid* (Wallach):

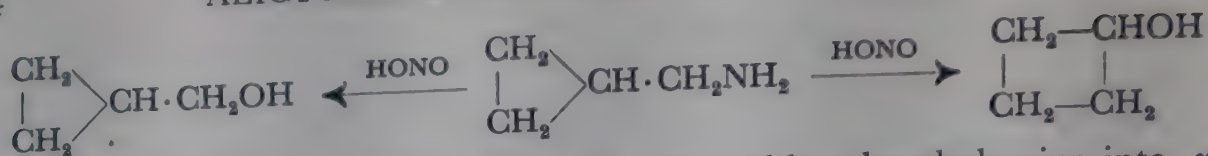


5. When CH_3MgI or $\text{C}_6\text{H}_5\text{MgBr}$ acts upon *o*-chloro*cycloheptanol*, ring contraction occurs to methyl*cyclohexylcarbinol*. The reaction perhaps takes the following course:

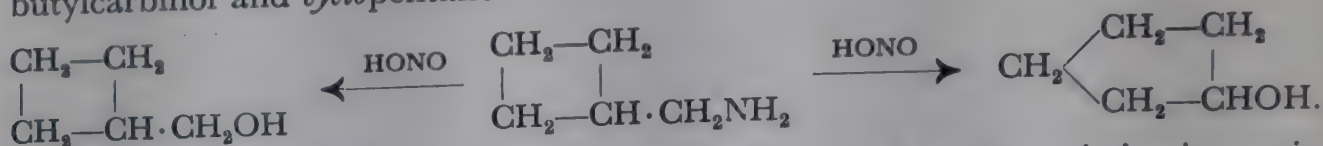


(b) METHODS OF RING EXPANSION

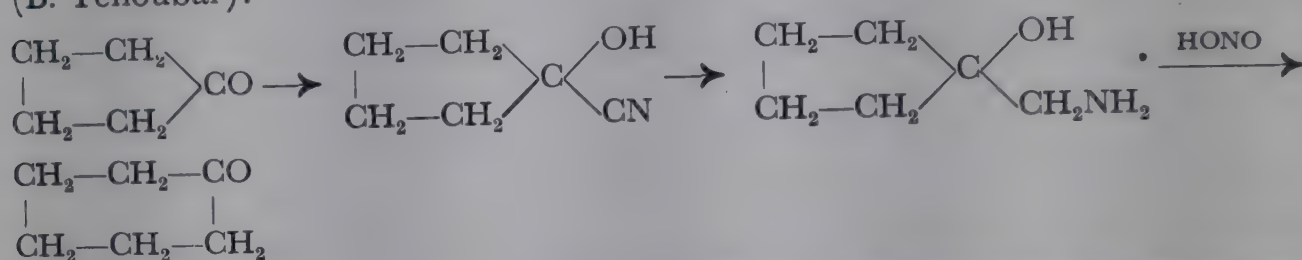
1. Under the action of nitrous acid *cyclopropylmethylamine* is converted partly into *cyclopropylcarbinol*, and partly into *cyclobutanol* (Demjanov):



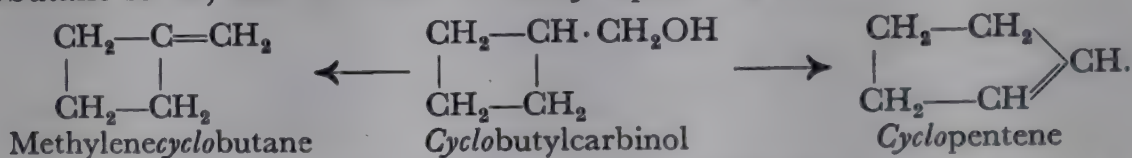
2. In a similar way, nitrous acid converts *cyclobutylmethylamine* into *cyclobutylcarbinol* and *cyclopentanol*:



3. By deamination of cyclic amino-alcohols with sodium nitrite in acetic acid, it is possible to produce cyclic ketones of the next higher ring system, e.g. (B. Tehoubar):

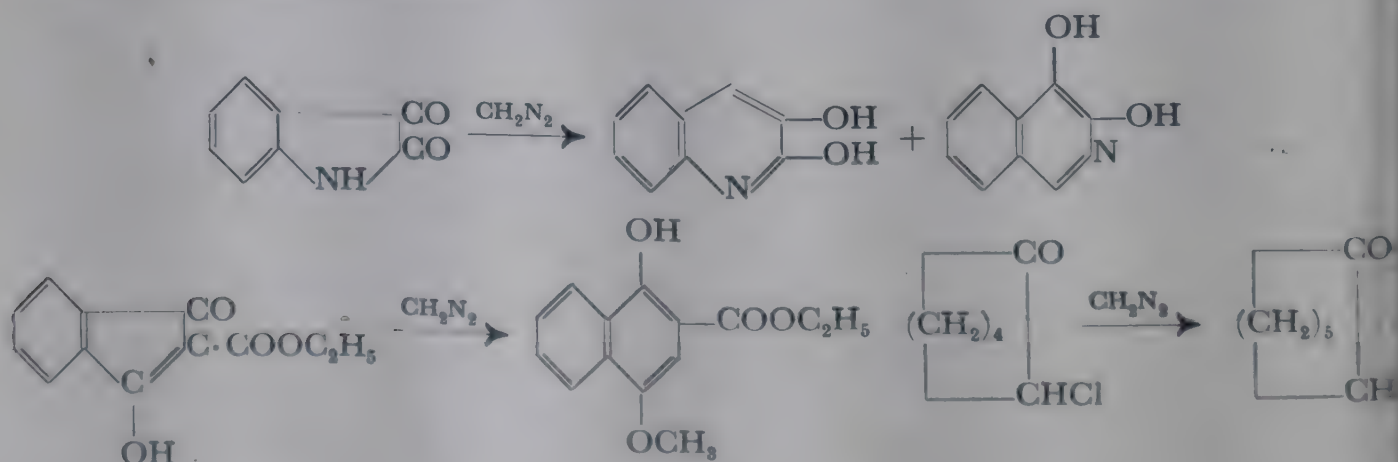


4. If water is split off from *cyclobutylcarbinol* by distillation with anhydrous oxalic acid, two unsaturated hydrocarbons are obtained, one belonging to the *cyclobutane* series, and the other to the *cyclopentane* series:

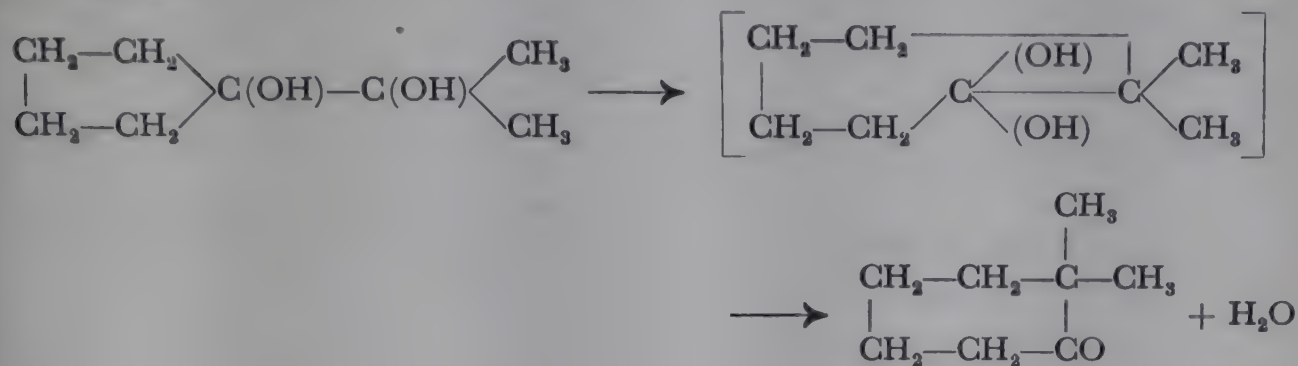


It is clear from the above examples that ring expansion often takes place if the side chain contains the group $-\text{CH}_2\text{NH}_2$ or $-\text{CH}_2\text{OH}$, whilst ring contraction is observed when certain reactive groups (NH_2, OH) are present in the nucleus. In any ring changes it is only one carbon atom that is included or eliminated.

5. Remarkable ring expansions are observed in the action of diazomethane on ketones, such as isatin, oxindone-carboxylic ester, and cyclic α -chloroketones. In the first case a mixture of 2:3-dihydroxyquinoline and 3:4-dihydroxyisoquinoline is produced. The carbon atom of the diazomethane has thus expanded the five-membered heterocyclic ring in isatin to a six-membered ring, by inserting itself between the pyrrole ring and the benzene ring, partly in the upper position and partly in the lower. In a similar way oxindone-carboxylic ester gives 1-hydroxy-4-methoxynaphthalene-2-carboxylic ethyl ester and α -chlorocyclohexanone gives α -chlorocycloheptanone:



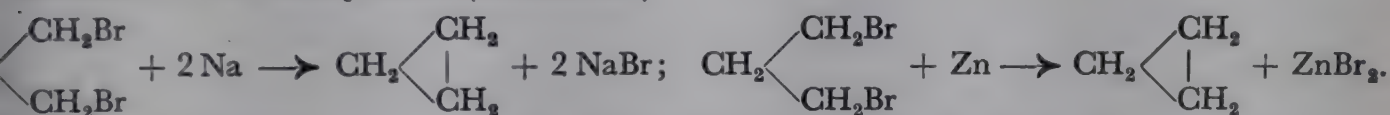
6. The isomerization of dimethylcyclohexanemethylene-glycol to a gem-dimethylcyclohexanone is more easy to follow than the above ring expansions. It occurs under the influence of aqueous oxalic acid, and is a special case of the pinacol rearrangement:



CHAPTER 51

CYCLOPROPANE AND ITS DERIVATIVES

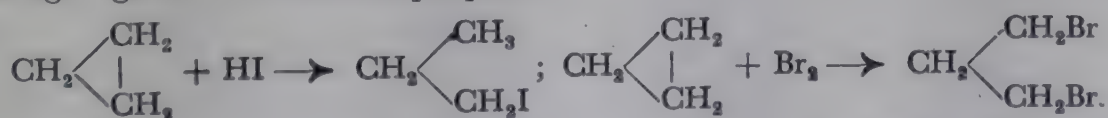
TRIMETHYLENE or CYCLOPROPANE is produced by the action of sodium on 1 : 3-dibromopropane (Freund), or by the action of zinc dust on an alcoholic solution of this compound (Gustavson):



The compound is a gas at ordinary temperatures, its boiling point being -34° , and melting point -126.6° . It is used as an anæsthetic. It is not attacked by cold potassium permanganate solution. Baeyer's permanganate reaction for double bonds is thus specific also in the presence of trimethylene derivatives. This is the more remarkable when it is remembered that the cyclopropane ring is comparatively easily ruptured.

Thus, cyclopropane is converted into propylene when passed through a red-hot tube. If catalysts (iron filings, platinum) are present the reaction takes place at much lower temperatures (e.g. $50-70^\circ$).

Hydrogen iodide breaks down trimethylene into iodopropane, and bromine in sunlight gives 1 : 3-dibromopropane:

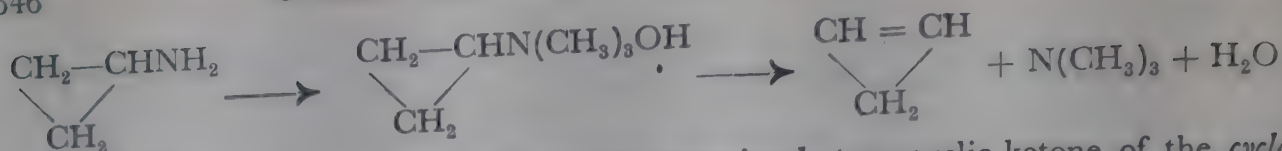


Chlorine substitutes in the cyclopropane molecule in diffuse daylight. The

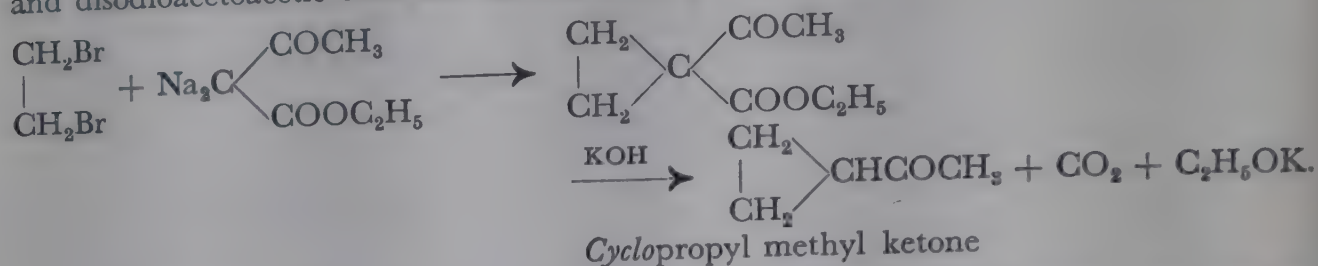
chlorocyclopropane, $\text{CH}_2 \begin{array}{c} \text{CH}_2 \\ \triangle \\ \text{CHCl} \end{array}$, thus produced, is a pleasant-smelling liquid boiling at 43° .

Various homologues of cyclopropane have been prepared in a similar way to the parent substance. On heating with zinc dust and dilute alcohol, for example, 1 : 3-dibromobutane gives methylcyclopropane (b.p. 4° to 5°), and 1 : 3-dibromo-2 : 2-dimethylpropane gives 1 : 1-dimethylcyclopropane (b.p. 21°).

Cyclopropene, a rather unstable compound of b.p.₇₄₄ -36° , was obtained by M. J. Schlatter from cyclopropylamine by exhaustive methylation:



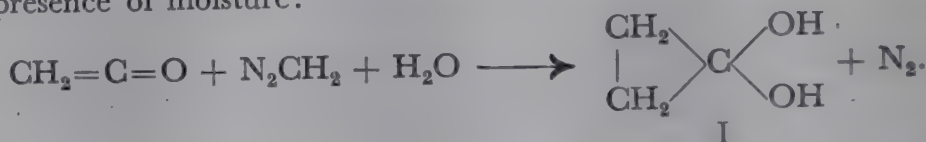
There are various methods of preparing the simplest exocyclic ketone of the *cyclopropane* series, *cyclopropyl methyl ketone*. In a process devised by Perkin jr. ethylene dibromide and disodioacetoacetic ester are used as starting materials:



The ketone boils at 112°. Hydrogen bromide breaks it down into methyl bromopropyl ketone:

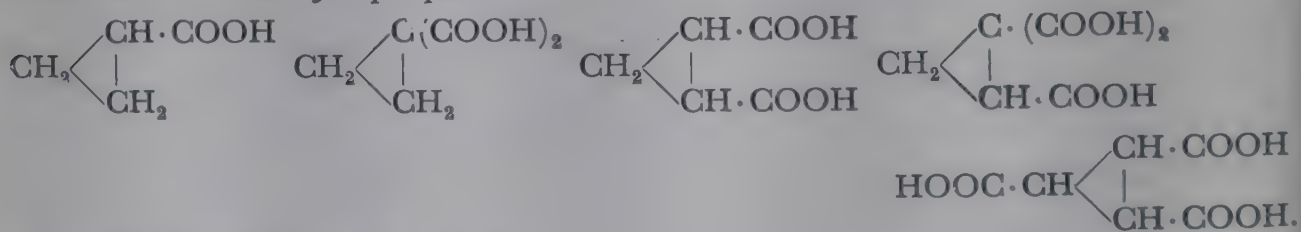


Cyclopropanone has been isolated as the hydrate (I) by the action of diazomethane on keten in the presence of moisture:



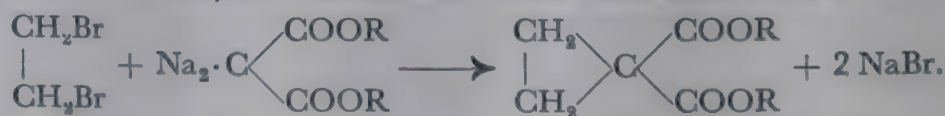
The compound is very unstable and is converted in a short time by isomerization into propionic acid. *Cyclopropanone* has not yet been isolated in the anhydrous state.

CYCLOPROPANECARBOXYLIC ACIDS. According to theory there should be one monocarboxylic acid, and two each of structurally isomeric di- and tricarboxylic acids derived from *cyclopropane*:

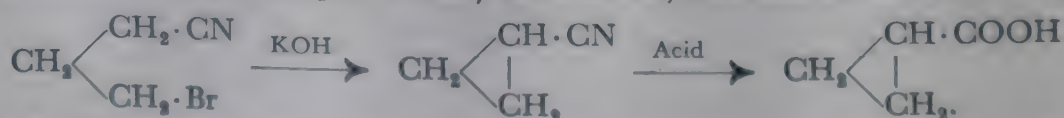


All these compounds are known.

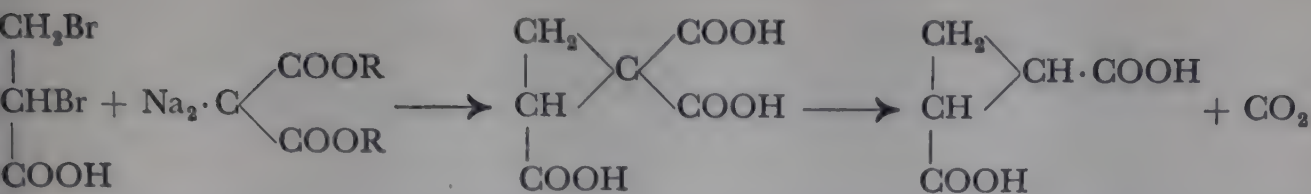
Cyclopropane-1:1-dicarboxylic acid is produced in the form of its ester by the condensation of ethylene dibromide with disodiummalonic ester:



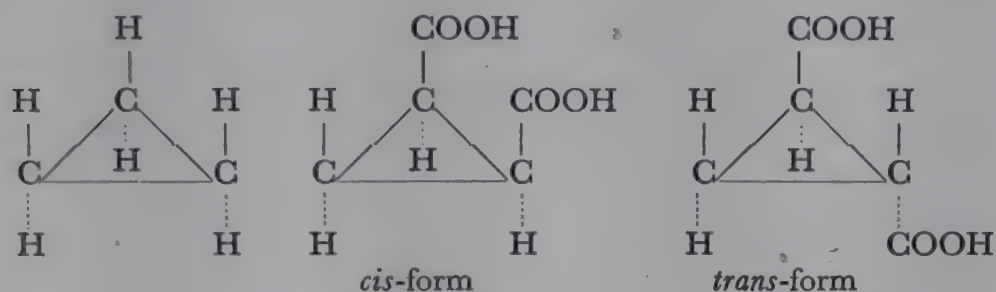
The free 1:1-dicarboxylic acid is broken down on heating, like most malonic acid derivatives. It loses on warming one molecule of carbon dioxide, and gives *cyclopropanemonocarboxylic acid* (m.p. 17°; b.p. 181°), which can also be obtained, for example, from γ -bromobutyronitrile in the following way:



Cyclopropane-1:2-dicarboxylic acid is obtained by splitting off carbon dioxide from *cyclopropane-1:1:2-tricarboxylic acid*. A convenient method of making the latter is the condensation of α,β -dibromopropionic acid with disodiummalonic ester:

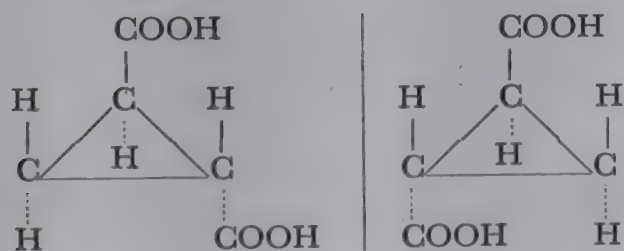


The three carbon atoms of *cyclopropane* must obviously lie in a plane, and of the six hydrogen atoms, three must lie above and three below this plane of the carbon atoms. Theory therefore requires the existence of two stereoisomeric 1:2-disubstitution products of *cyclopropane* (thus also for the 1:2-dicarboxylic acids). In one of these, both substituents are on the same side of the carbon plane, whereas in the stereoisomer one is in the upper plane of hydrogen atoms, and one in the lower:



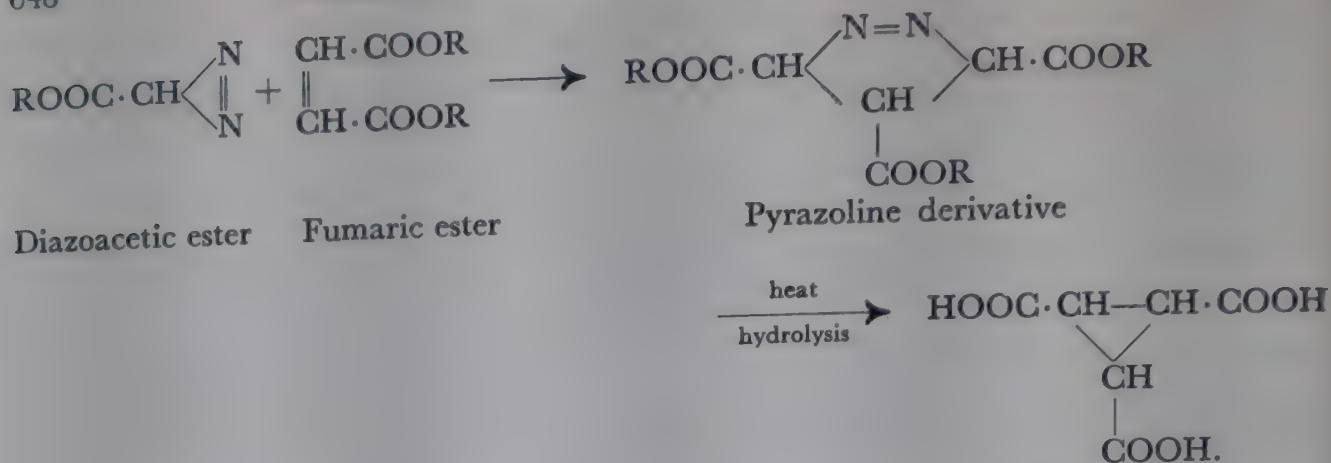
Both isomeric 1:2-dicarboxylic acids of *cyclopropane* are known. One of them melts at 139°, and is readily converted into an anhydride; the two carboxyl groups in this compound will therefore be spatially adjacent, i.e. on the same side of the plane of the carbon atoms. This is the *cis*-compound. The isomeric 1:2-dicarboxylic acid melts at 175°, and does not form an anhydride. It is the *trans*-acid.

Whilst the *cis-cyclopropane*-1:2-dicarboxylic acid is a symmetrical molecule, the *trans*-1:2-dicarboxylic acid, as the diagram shows, cannot be superimposed on its mirror image, and must therefore be resolvable into optically active forms:



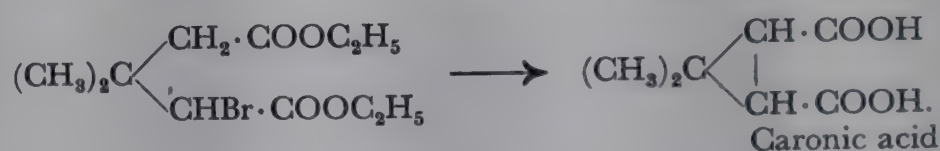
The resolution of racemic *cyclopropane*-1:2-dicarboxylic acid into its two enantiomorphous forms has been accomplished by E. Buchner by means of the brucine salts. The two antipodes have a specific rotation $[\alpha] = \pm 84.8^\circ$, and a melting point of 175°. The resolution of the *cyclopropane*-1:2-dicarboxylic acid of melting point 175° into optically active forms is an unequivocal proof that this acid is the *trans*-form.

Cyclopropane-1:2:3-tricarboxylic acid can be prepared by a process due to Buchner and Curtius. It depends upon the addition of diazoacetic ester (or diazomethane) to fumaric ester. A pyrazoline compound is thus produced, which on heating loses nitrogen and is converted into the 1:2:3-tricarboxylic acid of *cyclopropane*:

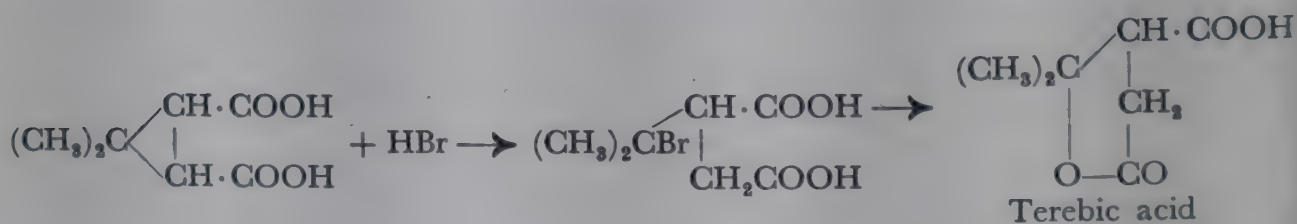


Cyclopropane-1:2:3-tricarboxylic acid also occurs in *cis-trans* isomeric forms. Homologous *cyclopropanecarboxylic acids* have been repeatedly obtained by the degradation of bicyclic camphors. Thus, *caronic acid* is formed by the oxidation of carone (see p. 696) which can be obtained synthetically. It is 2:2-dimethyl-*cyclopropane-1:3-dicarboxylic acid*, and is known in a *cis*- and a *trans*-form. The latter has been resolved into the enantiomorphous forms with a specific rotation of $\pm 38.5^\circ$.

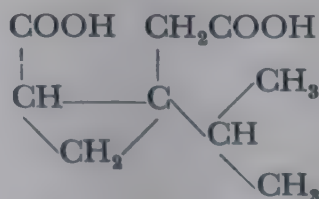
It can be synthesized, e.g. from α -bromo- β -dimethylglutaric ester by removing hydrogen bromide by means of alcoholic potash:



Hydrogen bromide ruptures the trimethylene ring in caronic acid. The bromine-containing intermediate product is readily converted into *terebic acid*, a decomposition product of oil of turpentine, or of its chief constituent, pinene:



α -*Tanacetonedicarboxylic acid* belongs to the rather more complex *cyclopropane-carboxylic acids*:

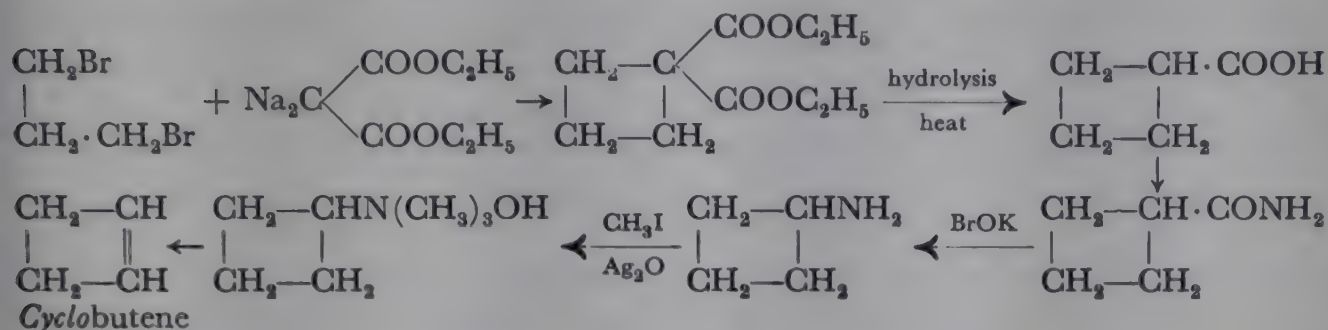


It is an oxidation product of the bicyclic ketone thujone (see p. 695).

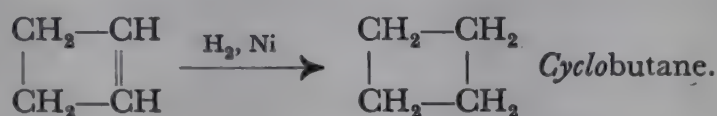
CHAPTER 52

CYCLOBUTANE AND ITS DERIVATIVES

CYCLOBUTANE and CYCLOBUTENE have been obtained by Willstätter, from trimethylene bromide and sodiomalonic ester in the following way:



If *cyclobutene* is passed with hydrogen over nickel at 100°, it is converted into *cyclobutane*:

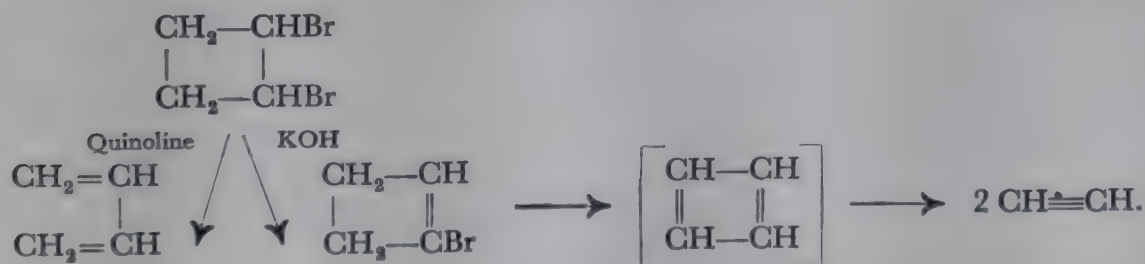


Both *cyclobutene* and the saturated *cyclobutane* are gases at room temperature. The latter liquefies at -15°. Whilst the unsaturated compound readily adds on bromine, and instantaneously reduces potassium permanganate, *cyclobutane* is indifferent towards hydriodic acid and permanganate in the cold. It is, however, reduced by hydrogen in the presence of nickel at 180° to butane, with opening of the ring.



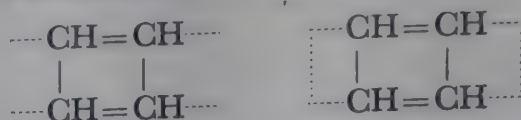
CYCLOBUTADIENE, $\begin{array}{c} | \quad | \\ \text{CH}=\text{CH} \end{array}$, has not yet been prepared. If 1:2-dibromo-

cyclobutane, which can be obtained from *cyclobutene* and bromine, is heated with quinoline, butadiene is formed together with higher molecular compounds. If attempts are made to remove hydrogen bromide from 1:2-dibromocyclobutane with powdered alkali, 1-bromocyclobutene-(1) is formed, one molecule only of hydrogen bromide having been eliminated. At higher temperatures (210°) this is decomposed by the caustic potash to acetylene:

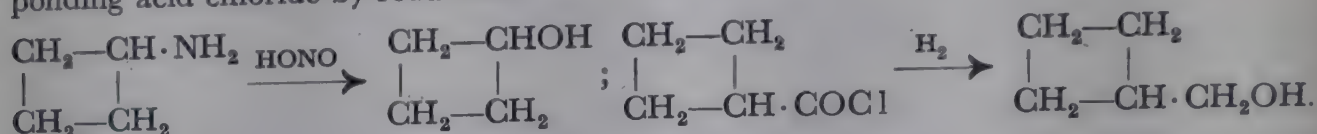


The negative result of the attempts to prepare *cyclobutadiene* shows that this compound must be exceedingly unstable, if it has any existence at all. This is noteworthy, because it follows that Thiele's explanation of the cause of the relatively saturated state of the benzene molecule (p. 378) does not hold in the *cyclobutane* series. If the partial valencies of two carbon atoms lying between two

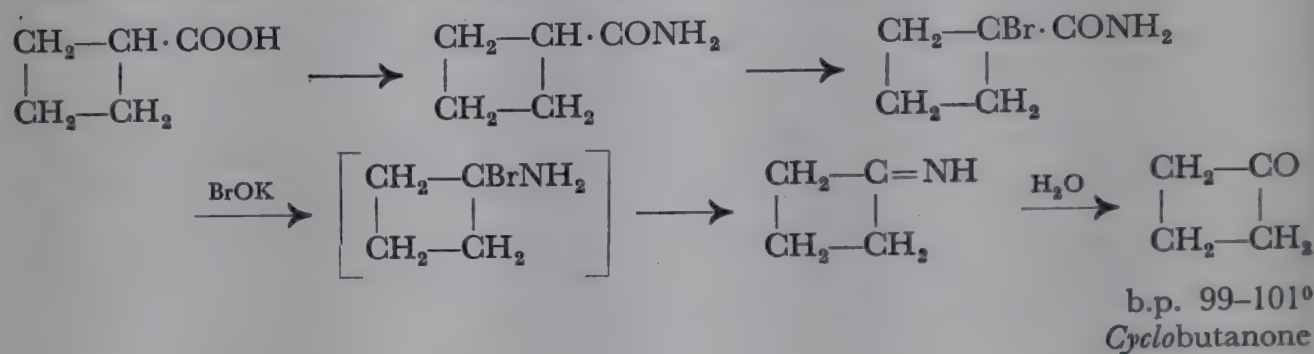
double bonds always saturated each other, one would expect *cyclobutadiene* to be a relatively saturated and stable substance:



Of the ALCOHOLS OF THE CYCLOBUTANE SERIES, the simplest representatives, *cyclobutanol* (b.p. 123°) and *cyclobutylcarbinol*, may be mentioned. The first is obtained by the action of nitrous acid on *cyclobutylamine*; *cyclobutylcarbinol* has been obtained from the corresponding acid chloride by reduction:



The simplest *esocyclic ketone* (carbonyl group in the ring) of the *cyclobutane* group is known. It was prepared by Kishner from *cyclobutanemonocarboxylic acid*, by first converting this into the amide, brominating the latter, and then submitting the compound to degradation by bromine and alkali. The individual stages of the reaction are shown in the following scheme:



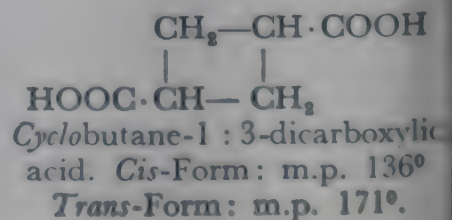
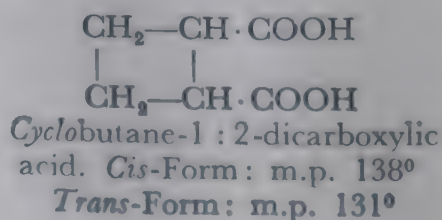
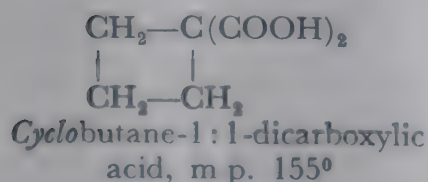
The constitution of *cyclobutanone* is proved by the fact that it is cleaved oxidatively by nitric acid to succinic acid.

In *acetylcyclobutane*, or *cyclobutyl methyl ketone*, we have the simplest *exocyclic ketone* of this series. The compound, which smells of peppermint, and boils at 134°, is prepared by the action of dimethylzinc on the chloride of *cyclobutanecarboxylic acid*:

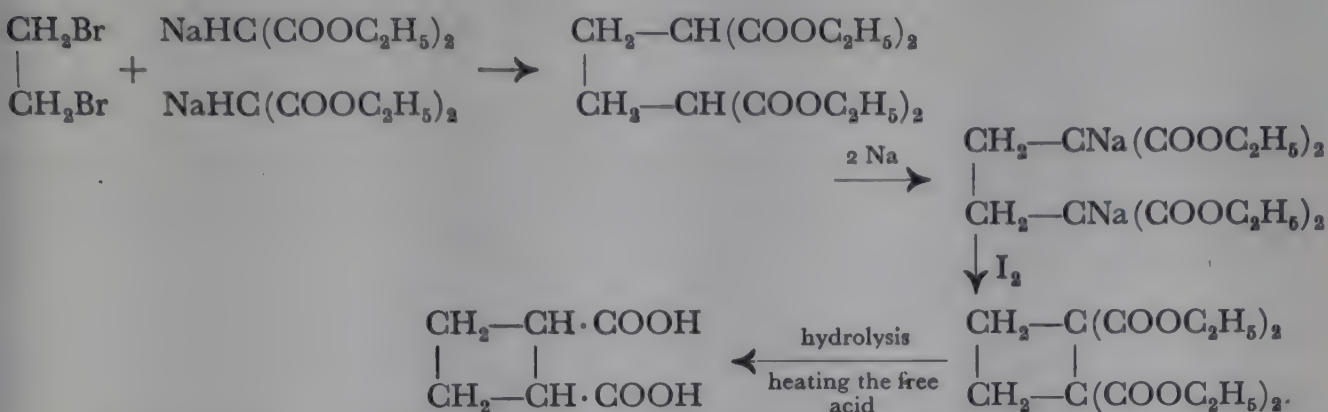


CYCLOBUTANECARBOXYLIC ACIDS. *Cyclobutanemonocarboxylic acid*, of which the synthesis from *cyclobutane-1:1-dicarboxylic acid* has already been mentioned, is an oil, boiling at 194°. It shows much similarity to the saturated fatty acids. It is converted into *n*-valeric acid by heating with hydriodic acid to 200°.

Theory predicts three structurally isomeric *cyclobutanedicarboxylic acids*. Of these the 1:2- and the 1:3-dicarboxylic acids must occur in a *cis*- and a *trans*-form each. All these isomeric compounds are known:



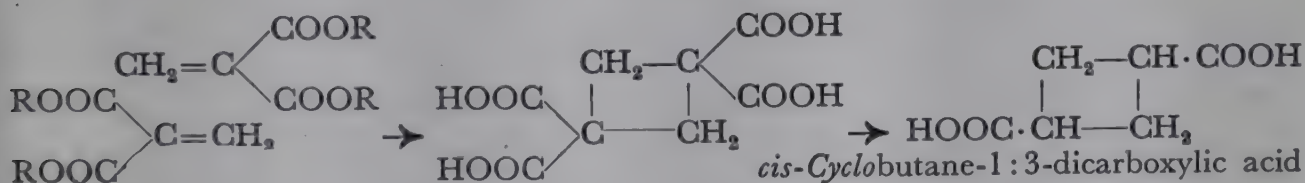
The synthesis of *cyclobutane-1:2-dicarboxylic acid* starts from ethylene dibromide and sodiomalonic ester:



For the preparation of *cyclobutane-1:3-dicarboxylic acid* a reaction may be used which is given by some ethylenic compounds. It is the polymerization, or combination of two molecules of an ethylenic compound to give a *cyclobutane* derivative. The process, which is often accelerated by warming, exposure to light, or the action of acids or alkalis, may be represented schematically as follows:

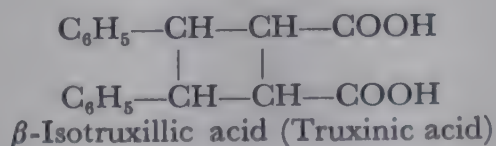
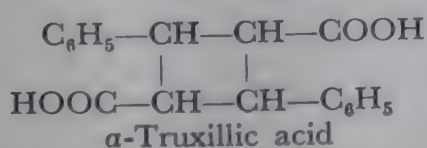


An example is the polymerization of methylenemalonic ester. This compound is converted by hydrolysis with alcoholic potash first into *cyclobutane-1:1:3:3-tetracarboxylic acid*, and then into *cis-cyclobutane-1:3-dicarboxylic acid*:



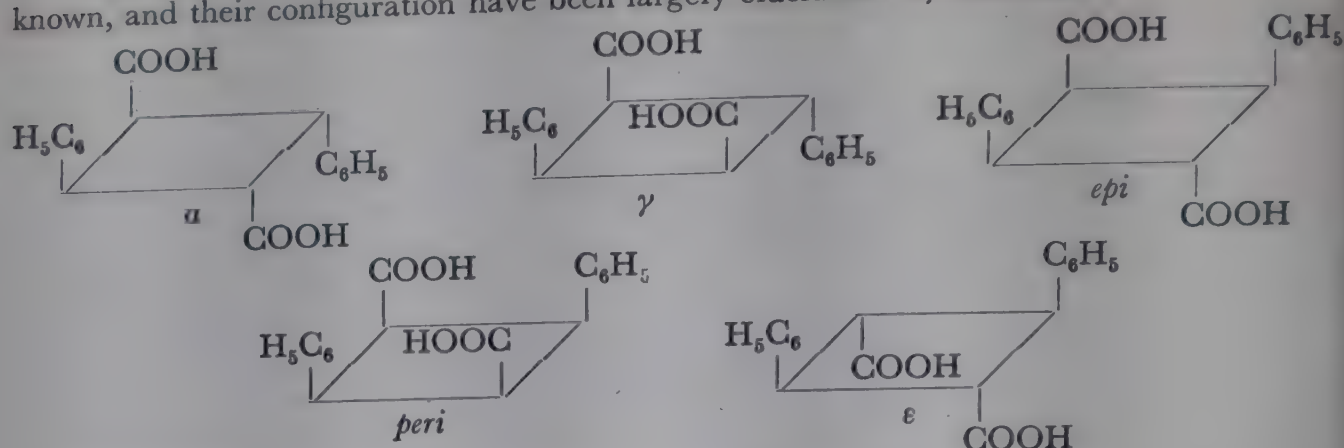
The *gem*-dimethyl derivative of this acid, *norpinic acid*, is a degradation product of α -pinene (see p. 697).

The *truxillic acids* and *isotruxillic acids* (or *truxinic acids*) are interesting and important phenylated *cyclobutanedicarboxylic acids*. α -Truxillic acid and β -isotruxillic acid are found in the coca-leaf, as constituents of the alkaloids accompanying cocaine. On hydrolysing these alkaloids they are set free. They possess the same composition as, but twice the molecular weight of cinnamic acid, and are converted into the latter by distillation. These facts, together with their saturated nature, and further, the property of β -isotruxillic acid of giving benzil on oxidation (which may be considered as conclusive evidence for the occurrence of the grouping $\text{C}_6\text{H}_5-\text{C}-\text{C}-\text{C}_6\text{H}_5$ in this compound) point to the following formulæ for α -truxillic acid and β -isotruxillic acid:

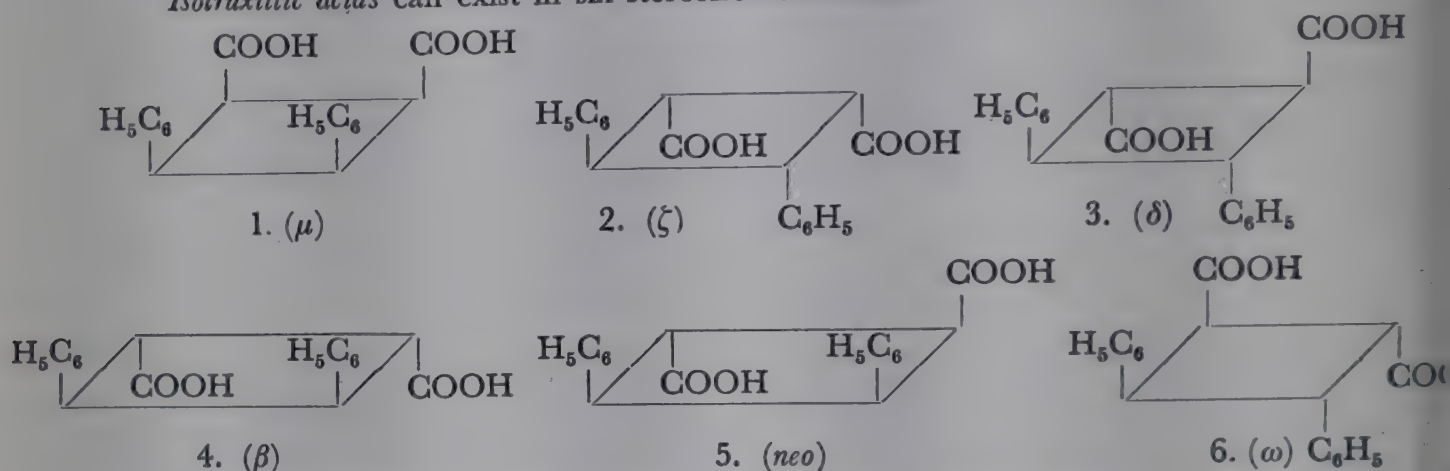


An excellent synthesis of α -truxillic acid consists in the exposure of ordinary cinnamic acid to light.

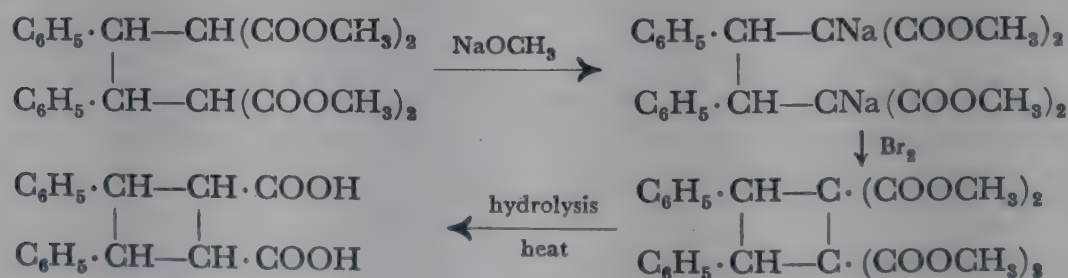
The truxillic and isotruxillic acids are also of considerable stereochemical interest. For the *truxillic acids*, five stereoisomerides come into consideration; all of them are known, and their configuration have been largely elucidated by Stoermer:



Isotruxillic acids can exist in six stereoisomeric forms:



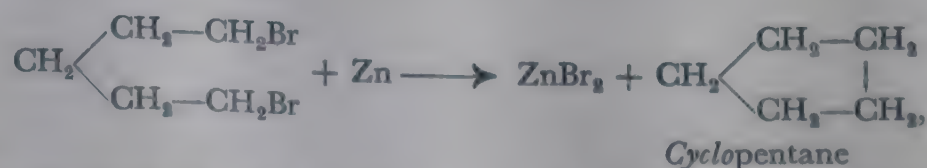
All the isotruxillic acids are known. The ζ - and δ -acids, for example, have been prepared from 2 : 3-diphenylbutane-1 : 1 : 4 : 4-tetracarboxylic ester by the following method:



CHAPTER 53

CYCLOPENTANE AND ITS DERIVATIVES

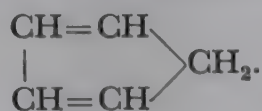
CYCLOPENTANE has been repeatedly detected as a constituent of Caucasian and American mineral oil. Synthetically it is prepared from 1 : 5-dibromopentane and zinc:



and also by reduction of the readily obtainable *cyclopentanone*.

It is a mobile liquid, boiling at 50.5°. It is indifferent towards bromine in the dark, but in the light it is substituted by this halogen, hydrogen bromide being evolved. The bromocyclopentane thus produced loses hydrogen bromide when treated with alcoholic potash, giving *cyclopentene*, $\text{CH}_2 \begin{array}{l} \diagup \text{CH}=\text{CH} \\ \diagdown \text{CH}_2-\text{CH}_2 \end{array}$, b.p. 45°, a compound with all the properties of an olefin.

A very interesting substance is *cyclopentadiene* (b.p. 41°):

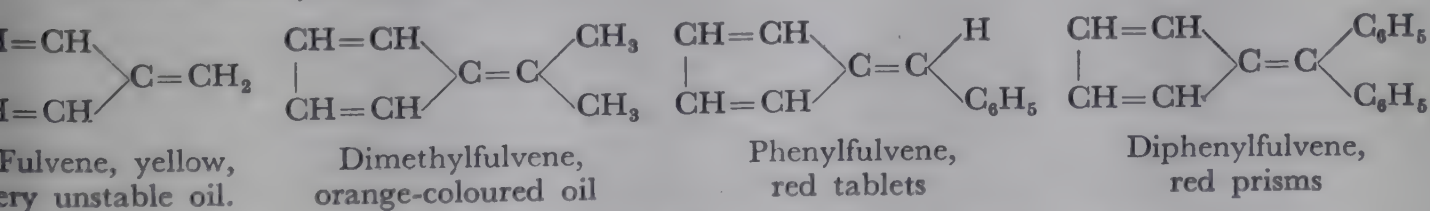


It occurs as a decomposition product of coal in crude benzene, and can be separated from the low-boiling fractions of the latter. It has also been discovered amongst the products of the thermal decomposition of paraffin oils. The hydrocarbon has been synthesized by Zelinsky. Bromine was added to *cyclopentene*, 1 : 2-dibromocyclopentane being formed. The latter was heated with fused sodium acetate and acetic acid to 182°, when it lost two molecules of hydrogen bromide.

The system of conjugated double bonds which is contained in *cyclopentadiene* endows it with an exceedingly unstable and reactive nature. It polymerizes even at ordinary temperatures to dicyclopentadiene, $\text{C}_{10}\text{H}_{12}$ (b.p. 170°), a dimeric compound, which partially breaks down again into *cyclopentadiene* on distillation, but, on the other hand, on heating to a higher temperature is converted into an amorphous, insoluble, high-polymeric substance.

The CH_2 -group of *cyclopentadiene* is characterized by great reactivity. Its hydrogen can be replaced by potassium. Methylmagnesium salts decompose *cyclopentadiene* producing methane. Specially noteworthy, however, is its reaction with aldehydes and ketones to give a group of coloured hydrocarbons, the **fulvenes**, of which Thiele made a through investigation.

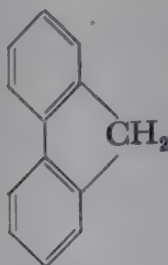
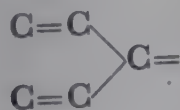
The condensation of aldehydes and ketones with *cyclopentadiene* occurs in alkaline solution (sodium ethylate, alcoholic potash). The simplest fulvene, derived from formaldehyde, is so unstable that it has not yet been isolated in the pure state. However, the fulvenes obtained, for example, from *cyclopentadiene* and acetone, methyl ethyl ketone, benzophenone, benzaldehyde, anisaldehyde, and cinnamic aldehyde, are well characterized.



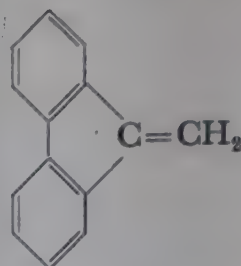
The deep colours of these fulvene hydrocarbons are due to the accumulation of double bonds and their special positions (multiply conjugated). Their great tendency towards polymerization and autoxidation can be traced to the same cause. They absorb oxygen very readily, and in that respect recall the behaviour of the yellow, naturally-occurring hydrocarbons, the carotenoids (see p. 708).

The same system of double bonds which is present in the fulvenes occurs also in the condensation products of fluorene and indene with aldehydes and ketones.

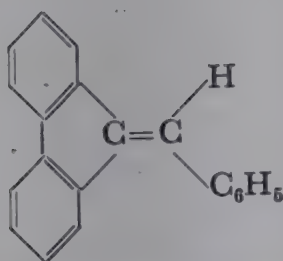
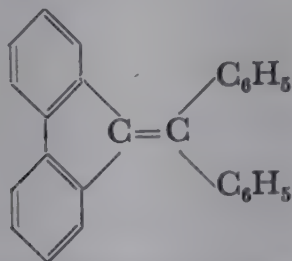
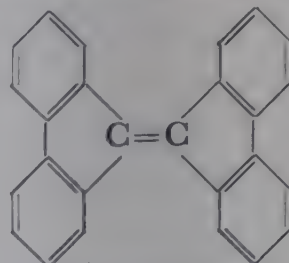
Some of these, especially those substituted with phenyl radicals, accordingly also possess colour:



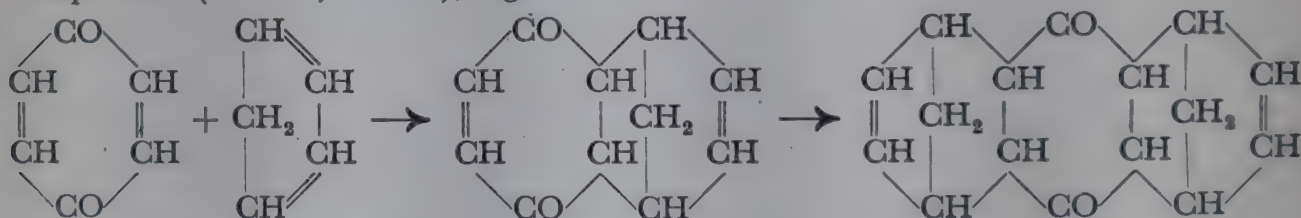
Fluorene



Biphenyleneethyne, colourless

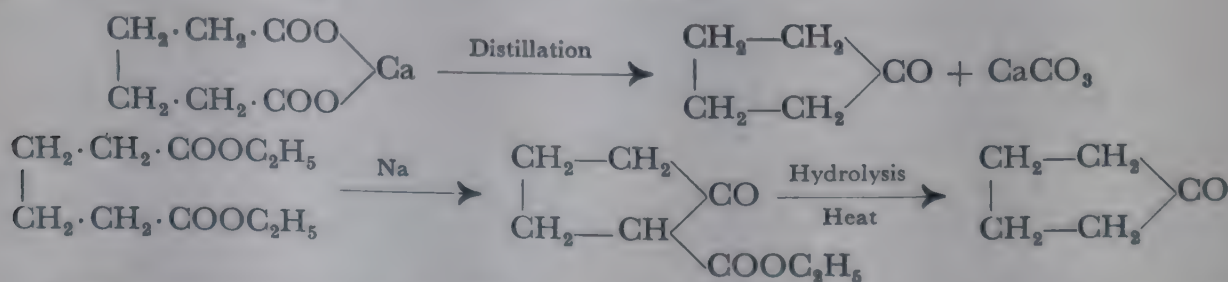
Phenylbiphenyleneethyne,
yellow in solutionDiphenylbiphenyleneethyne,
yellow in solutionDibiphenylene-
ethyne, red.

A new group of condensation reactions of *cyclopentadiene* was discovered by O. Diels and Alder. The hydrocarbon can add on, at the two ends of its system of conjugated double bonds, many unsaturated molecules, such as *p*-quinone, maleic acid, maleic anhydride, etc., giving rise to a large number of polycyclic compounds (diene synthesis), e.g.:

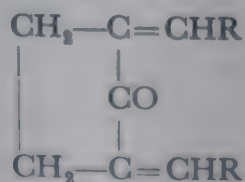
Endomethylene derivative of a
hydrogenated naphthoquinone

Ketones of the cyclopentane series. CYCLOPENTANONE is formed in small quantities by the dry distillation of wood, and collects in the residue in the subsequent rectification of the wood-spirit fraction.

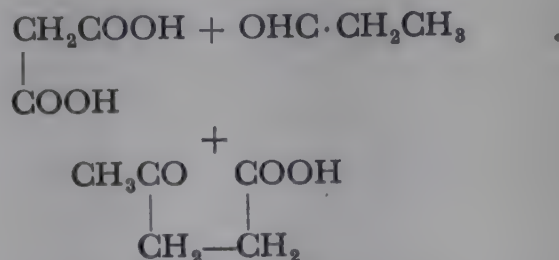
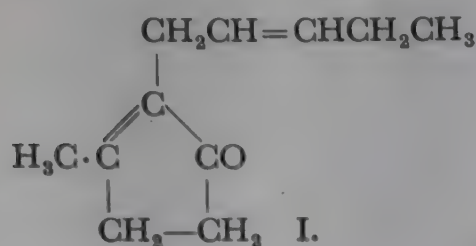
The ketone is synthesized from adipic acid, by dry distillation of its calcium salt, or by condensing its esters with sodium:



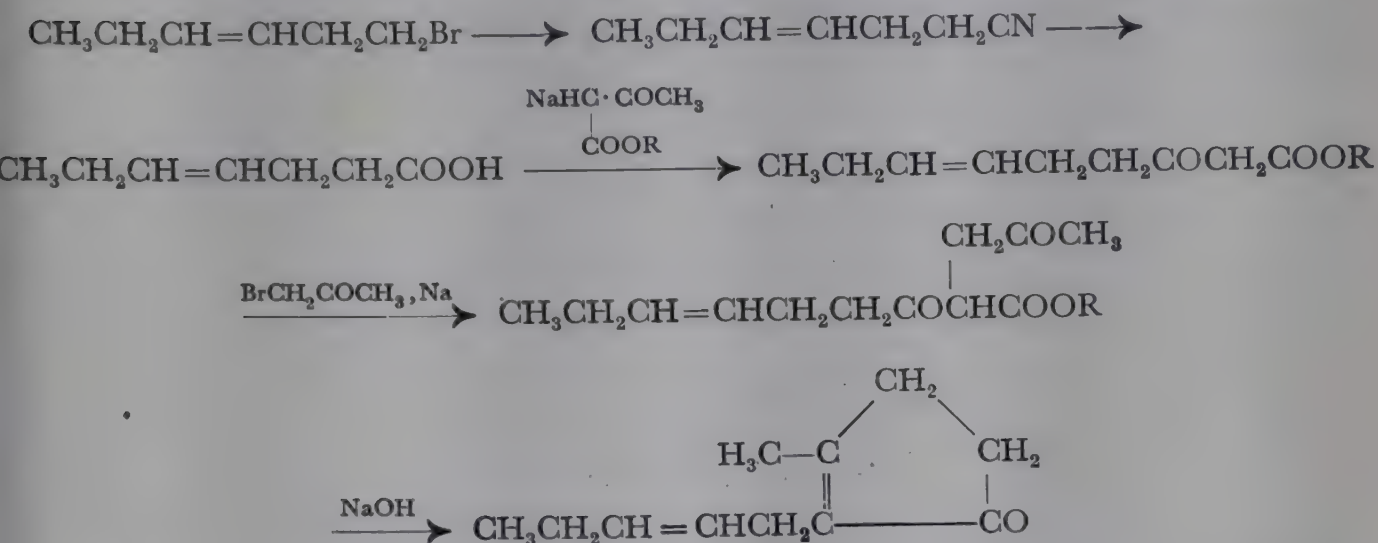
Cyclopentanone boils at 129°, and is converted by partial reduction into *cyclopentanol*, and by condensation with aldehydes into compounds of the type:



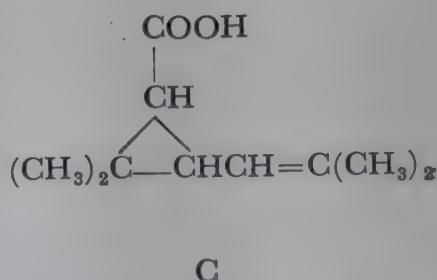
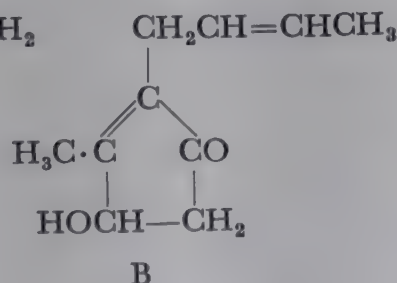
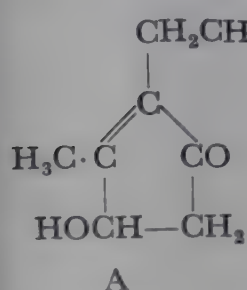
Derivatives of *cyclopentanone* are found amongst natural products. *Jasmone*, a perfume from jasmine oil, is an unsaturated ketone of the formula (I). It gives on oxidation propionaldehyde, malonic acid, and lævulinic acid:



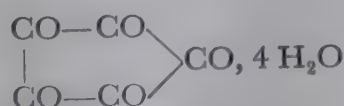
Hunsdiecker succeeded in obtaining jasmone synthetically in the following way:



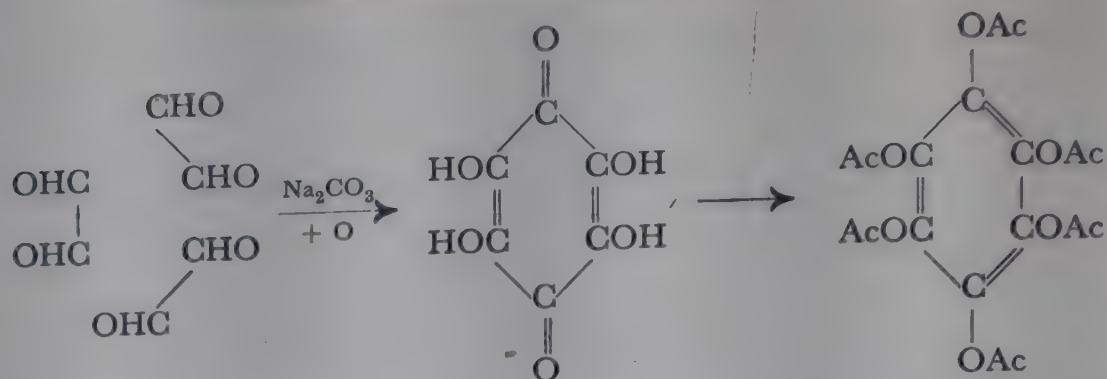
Closely related to jasmone are *pyrethrolone* (A) and *cinerolone* (B), which, in the form of esters, are constituents of pyrethrum blossoms (*Chrysanthemum cinerariifolium* Bocc.). The latter are used as insect powders. Such an ester is pyrethrin I, composed of pyrethrolone and chrysanthemum-monocarboxylic acid (C) (F. R. La Forge).



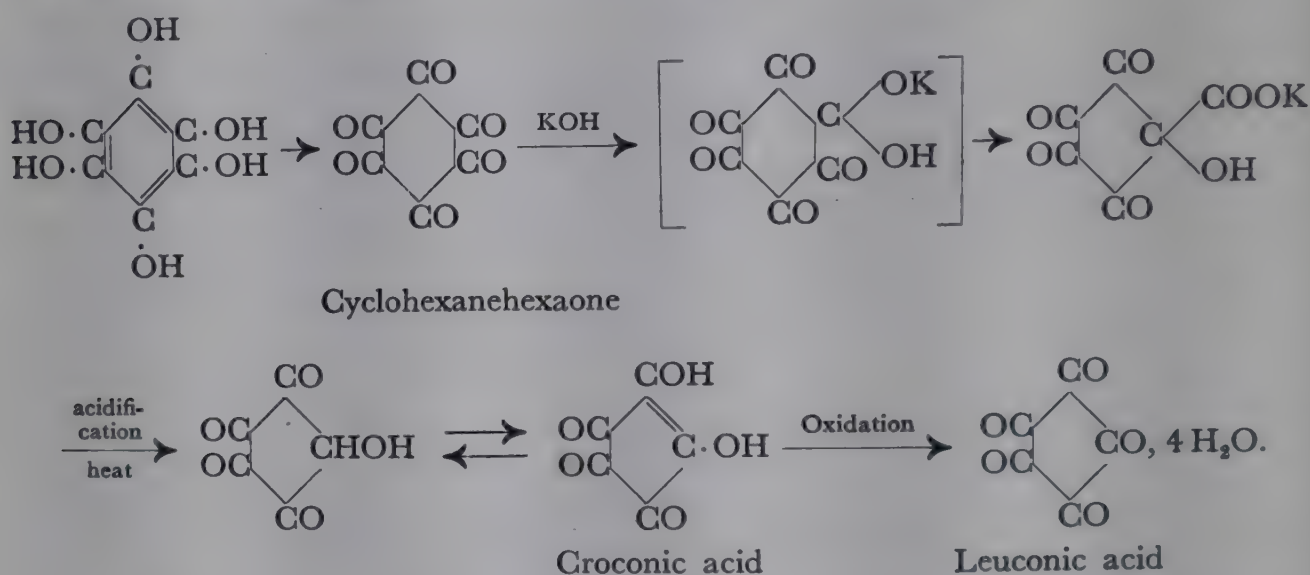
Cyclopentanepentaone, the so-called "*leuconic acid*", is very interesting. It is obtained, *via* an intermediate product, *croconic acid*, from hexahydroxybenzene, in the hydrate form,



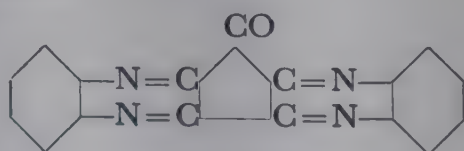
Hexahydroxybenzene, which was formerly prepared from carbon monoxide and potassium, or from triquinoyl (cf. p. 442) is now readily obtainable by a new process due to Homolka. Tetrahydroxyquinone which is readily made from the bisulphite compound of glyoxal and sodium carbonate, is converted into the hexacetate of hexahydroxybenzene by means of acetyl chloride and zinc:



If hexahydroxybenzene is oxidized in alkaline solution, *cyclohexanehexaone* ("triquinoyl") is first produced, but then undergoes a "benzilic acid rearrangement" being thereby converted into croconic acid. The alkali salts of the latter are deep yellow. Oxidation of croconic acid gives leuconic acid:



The above constitution for leuconic acid is supported, for example, by the facts that (a) it gives a pentoxime with hydroxylamine, (b) it reacts with aromatic *ortho*-diamines to give diazines,



which still contain one free carbonyl group, detectable by the usual reagents, and particularly (c) it gives mesoxalic acid and glyoxal on hydrolysis with sodium carbonate:



Carboxylic acids of the cyclopentane series. The "naphthenic" acids of Russian mineral oil contain, in addition to complex acid compounds, simple alicyclic monocarboxylic acids. Markovnikov separated a methylcyclopentane-monocarboxylic acid from them, and J. v. Braun recently isolated further acids of the *cyclopentane* series ([3:3:4-trimethyl-1-cyclopentyl]-acetic, -butyric, and -valeric acids).

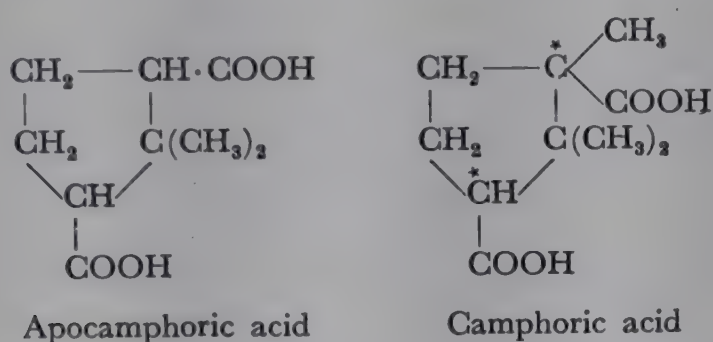
Cyclopentanemonocarboxylic acid, which is readily obtained by heating the 1:1-dicarboxylic acid:



boils at 214–215°, and has an unpleasant smell, not unlike that of valeric acid.

Theory requires the existence of a *cis*- and a *trans*-form for the 1:2-dicarboxylic acid, and both are known. The *cis*-form melts at 140°, readily gives an anhydride, and can be rearranged to the *trans*-compound by heating with hydrochloric acid to 180°. The latter (m.p. 160°) does not form an anhydride. When it is dehydrated it gives the anhydride of the *cis*-acid.

APOCAMPHORIC ACID and particularly CAMPHORIC ACID, a degradation product of Japan camphor,



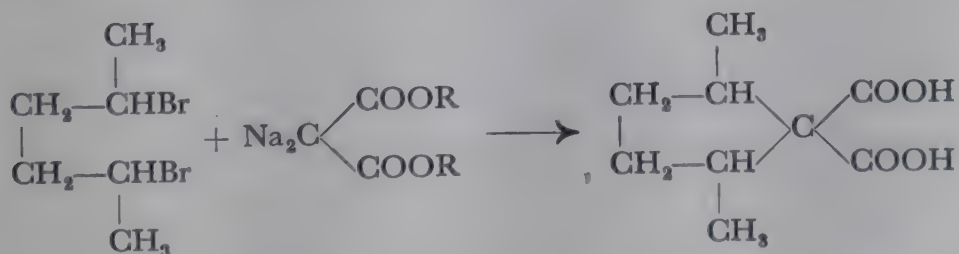
are important methyl derivatives of *cyclopentane*-1 : 3-dicarboxylic acid.

Camphoric acid has two asymmetric carbon atoms (marked in the formula by asterisks). The four optically active isomeric forms required by theory are known.

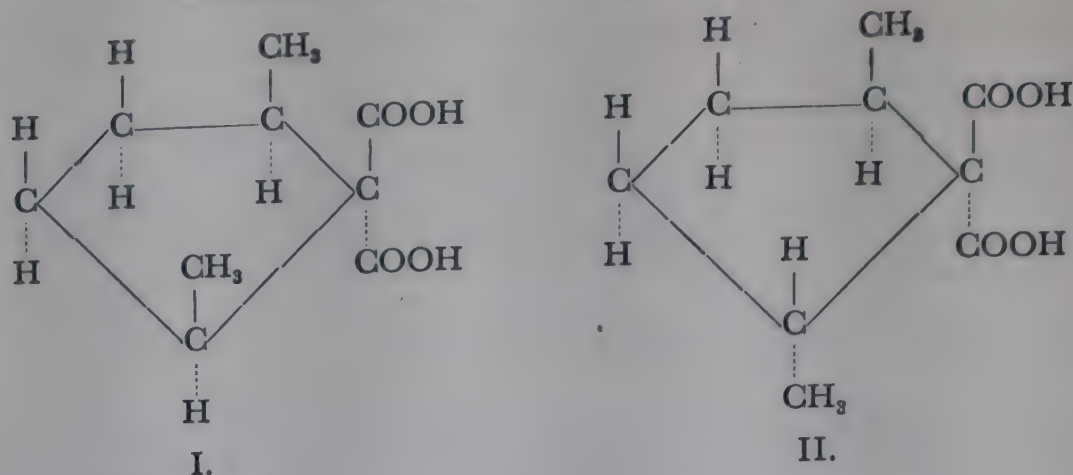
The two enantiomorphous *cis*-compounds, which have the carboxyl groups on the same side of the plane of the *cyclopentane* carbon atoms, are known as *d*- and *l*-camphoric acid. They melt at 187°, have a specific rotation of 47.8°, and form anhydrides. The two possible *trans*-acids are the *d*- and *l*-isocamphoric acid. They melt at a lower temperature, 171°; $[\alpha]_D = 48^\circ$.

For the synthesis of *dl*-camphoric acid, see pp. 699–701.

A new method of determining the configuration of *cis-trans* isomerides is encountered with the 2:5-dimethyl*cyclopentane*-1:1-dicarboxylic acids. These are obtained by the condensation of 2:5-dibromohexane with disodiummalonic ester



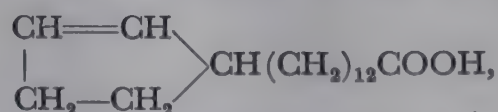
in the two possible stereoisomeric forms (I) and (II) (racemate), of which the configurations are shown below:



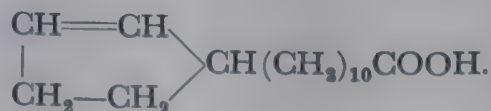
If one molecule of carbon dioxide is eliminated from compound I, presumably two isomeric dimethylcyclopentanemonocarboxylic acids will result, since either the upper or the lower carboxyl group can be removed. From the dicarboxylic acid (II), only one (racemic) monocarboxylic acid can be formed in either case, since the exit of the upper carboxyl group must lead to the same product as that of the lower group.

To determine the configuration of the two 2 : 5-dimethylcyclopentane-1 : 1-dicarboxylic acids it is thus only necessary to see what reaction products are obtained on heating. It was found by experiment that the dicarboxylic acid melting at 192–194° gives two isomeric monocarboxylic acids (m.p. 75–77°, and 26–30°, respectively); the other dicarboxylic acid melting at 204–205°, on the other hand, gives only one monocarboxylic acid, melting at 49.5°. The first dicarboxylic acid (m.p. 192–194°) must therefore have the configuration (I), and the second (m.p. 204–205°) formula (II) (Wislicenus).

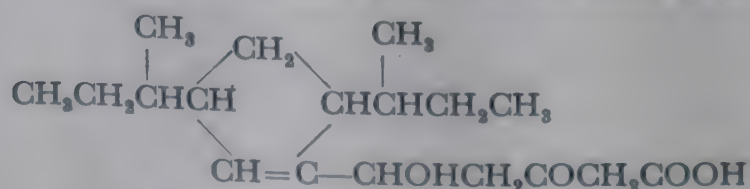
CHAULMOOGRIC ACID is an unsaturated higher acid of the cyclopentane series:



which is found in large quantities in chaulmoogra oil (oil from the seeds of species of *Hydnocarpus*). It melts at 68°, and boils at 247° (20 mm). It has recently met with considerable therapeutic interest since it has proved to be an active agent in the treatment of leprosy. The acid itself, and many of its derivatives, have been obtained synthetically. *Hydnocarpic acid* is another substance which is very active therapeutically:

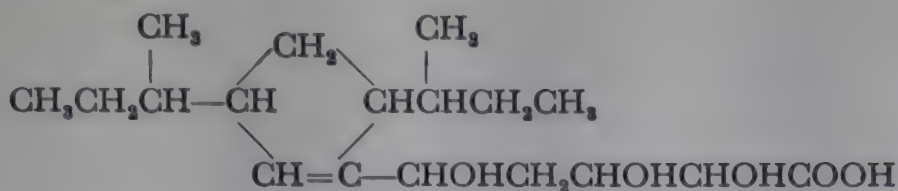


According to Kogl the plant-growth substance¹, AUXIN *b*, is a carboxylic acid, having a substituted cyclopentene ring. The formula proposed is as follows:

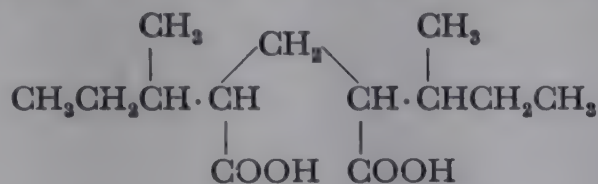


¹ GERHARD SCHLENKER, *Die Wuchsstoffe der Pflanzen. Ein Querschnitt durch die Wuchshormonforschung*, Munich, (1937). — F. W. KENT and K. V. THIMANN, *Phytohormones*, New York, (1937).

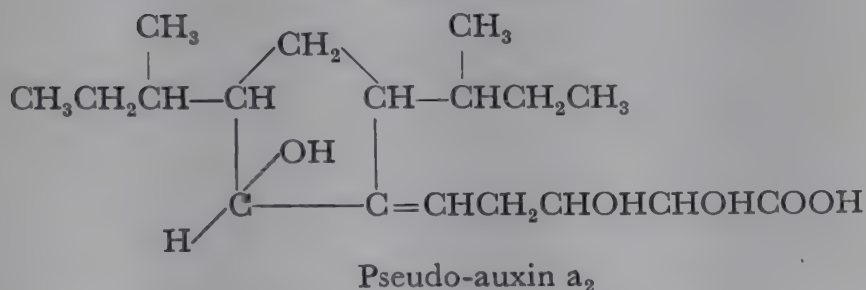
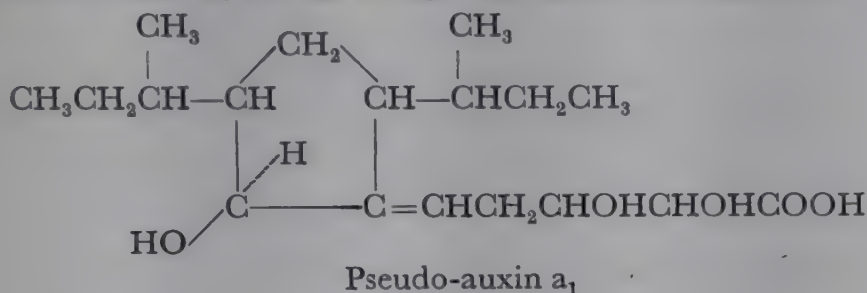
Auxin *a* has been given the formula:



Both compounds can be degraded to give a dicarboxylic acid (α,α' -di-*sec.*-butyl-glutaric acid):



After being kept for a few months, the auxins lose their activity. Auxin *a* then changes into pseudo-auxins a_1 and a_2 , owing to an allylic rearrangement.



Auxin *a* readily forms a lactone. This changes very rapidly, when irradiated by light of short wave-length, into a compound (lumi-auxone *a*), which no longer stimulates growth. The same transformation takes place in the presence of carotenoids under the influence of visible light.

CHAPTER 54

CYCLOHEXANE AND ITS DERIVATIVES (EXCLUDING AROMATIC COMPOUNDS)

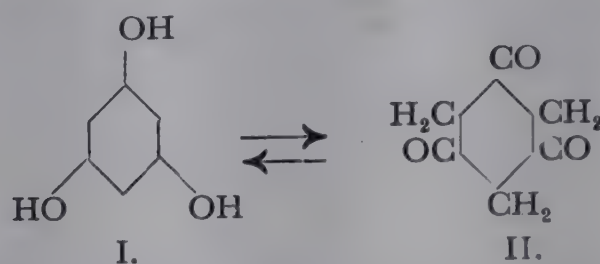
Connections between cyclohexane derivatives of aromatic and alicyclic character

Benzene and its derivatives are, formally speaking, *cyclohexatriene* compounds. The properties of the benzene derivatives, however, hardly agree with those expected *a priori* of *cyclohexane* derivatives with three double bonds, and an attempt has been made in an earlier part of this book (pp. 373, 377ff.) to explain the relatively saturated state of the aromatic compounds.

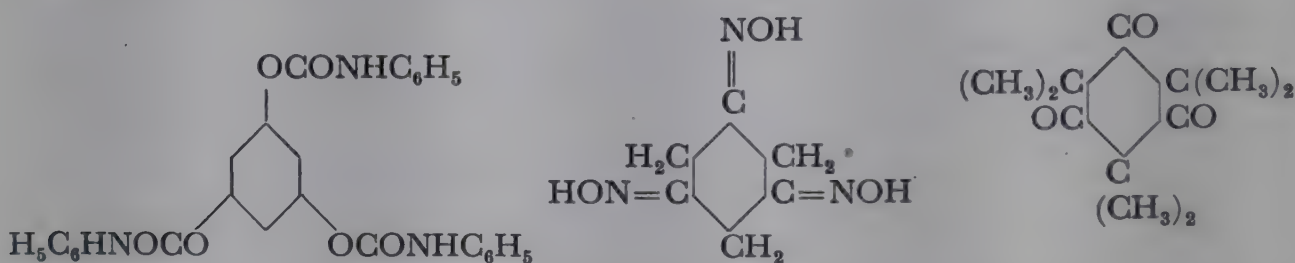
The investigations of the last decades have, however, done much to lessen and bridge what were formerly very sharp boundaries between benzene derivatives and hydroaromatic substances of the *cyclohexane* type. Numerous ways were

found by which compounds of the one series could be converted into those of the other. The character of the aromatic compounds as being of comparatively saturated character has also gradually lost in significance, since the perfection of preparative methods has shown that the addition of other atoms or groups to benzene derivatives often takes place quite rapidly and with great ease. In spite of this, however, benzene and its analogues have sufficient peculiarities to justify their being dealt with in a separate section, apart from the alicyclic compounds.

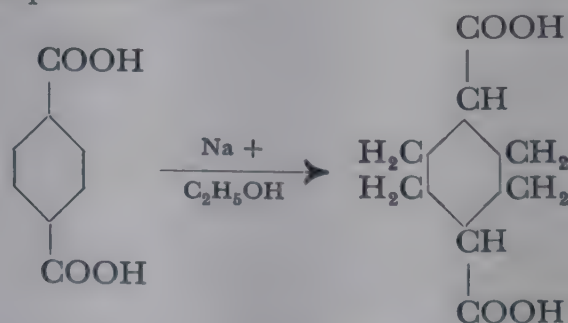
Some *cyclohexane* derivatives are tautomeric substances, capable of reacting on the one hand as benzene derivatives and on the other as alicyclic compounds. An example of this is phloroglucinol, of which the reactions are explained partly by the first and partly by the second of the following formulæ:



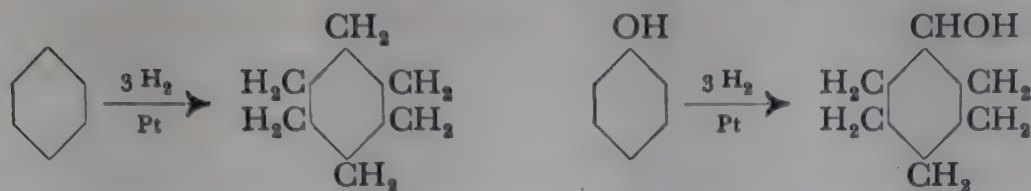
O-acyl derivatives, for example, are derived from formula I, and a trioxime and C-alkyl derivatives from formula II:



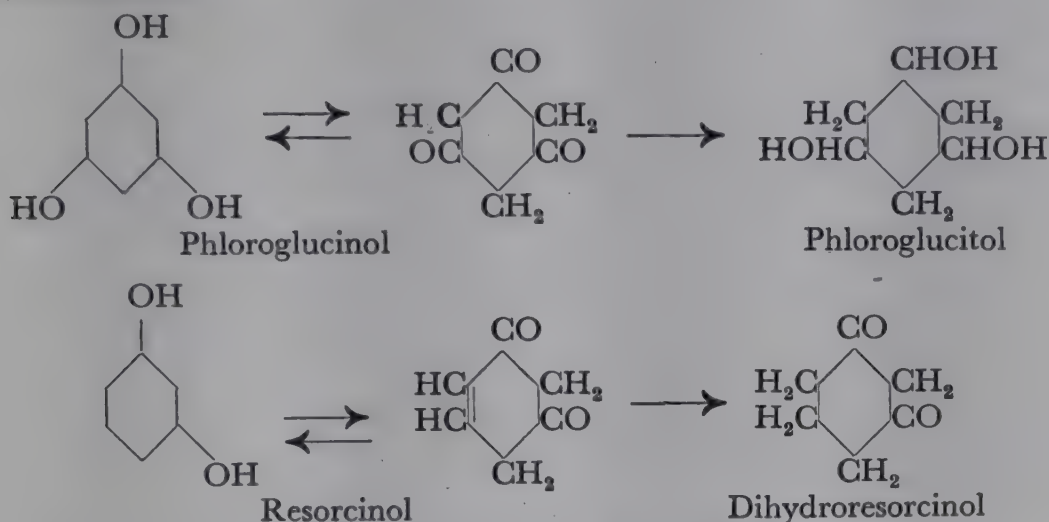
It is often fairly easy to convert aromatic compounds into hydroaromatic ones by reduction. Formerly sodium and alcohol (or amyl alcohol) were used for these reductions, and in the hands of A. von Baeyer and others, the method was used for the preparation of many hydroaromatic substances, e.g. hexahydrophthalic acid and hexahydroterephthalic acid:



In more recent times the hydrogenation of aromatic compounds has been carried out preferably with hydrogen and nickel at elevated temperatures (Sabatier), or with hydrogen and platinum or palladium (Paal, Skita, Willstätter). In the latter case the reaction may usually be carried out even at ordinary temperatures. The aromatic compound used must, however, be exceedingly pure if the hydrogenation is to take place smoothly. In this way, for instance, benzene can be converted into *cyclohexane*, phenol into *cyclohexanol*, etc.:



The polyhydric phenols with hydroxyl groups in the *meta*-positions take a special place amongst aromatic compounds in regard to the ease with which they are reduced to saturated *cyclohexane* compounds. This is connected with their ability to react in tautomeric forms. Their carbonyl forms, in consequence of their unsaturated hydroaromatic nature, are particularly strongly inclined to add on hydrogen. Thus, phloroglucinol is reduced even by sodium amalgam in aqueous solution to phloroglucitol, the symmetrical trihydroxycyclohexane and resorcinol to dihydroresorcinol:

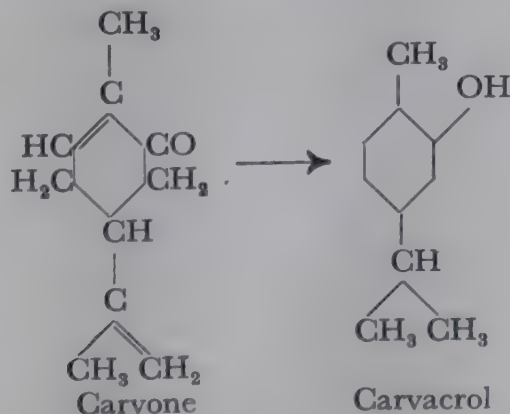


For the conversion of *cyclohexanol* into benzene, see p. 385–86.

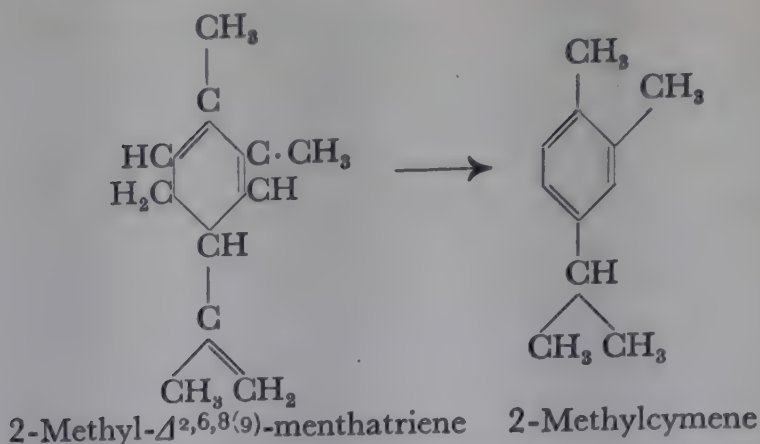
The conversion of aromatic into hydroaromatic compounds can also, under certain conditions, be brought about by oxidation. The best known example of this kind is the oxidation of *hydroquinones* to *quinones*. The latter are derivatives of *cyclohexadiene*, and as such do not possess aromatic properties.

The reverse process of reduction of the quinone to a benzene derivative takes place just as readily as the conversion of hydroquinone into quinone.

Some derivatives of *cyclohexane* of alicyclic nature can isomerize, more or less easily, into benzene derivatives, e.g. *carvone*, which by heating with formic acid or phosphoric acid is converted into *carvacrol*:



2-Methyl- $\Delta^{2:6:8(9)}$ -menthatriene (see p. 674), a hydrocarbon obtained by Klages from carvone (see p. 685), is converted, on heating with glacial acetic acid containing hydrogen chloride, into 2-methylcymene:

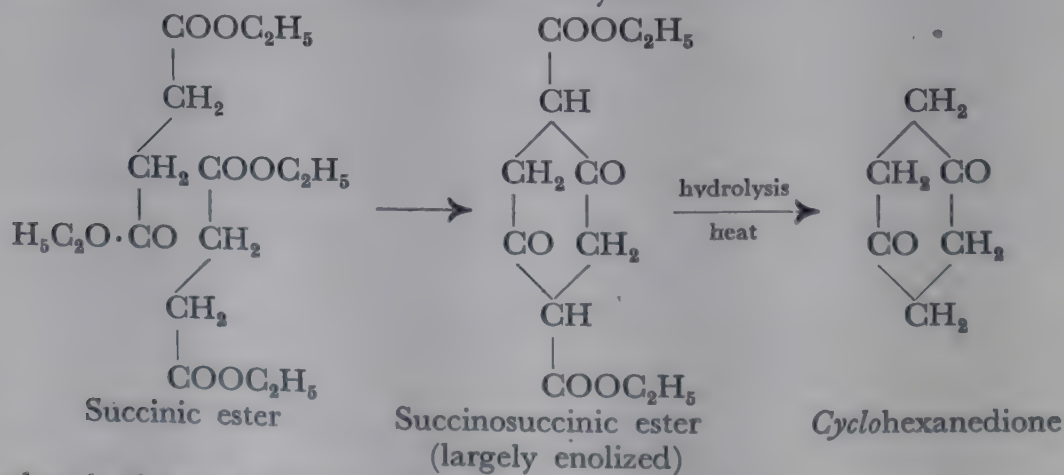


Cyclohexene and *cyclohexadiene* disproportionate to give benzene and *cyclohexane* when passed over palladium- or platinum-black even at 35° , and more rapidly on stronger heating; limonene, when passed over platinized charcoal at 140° , gives *p*-cymene and *p*-menthane.

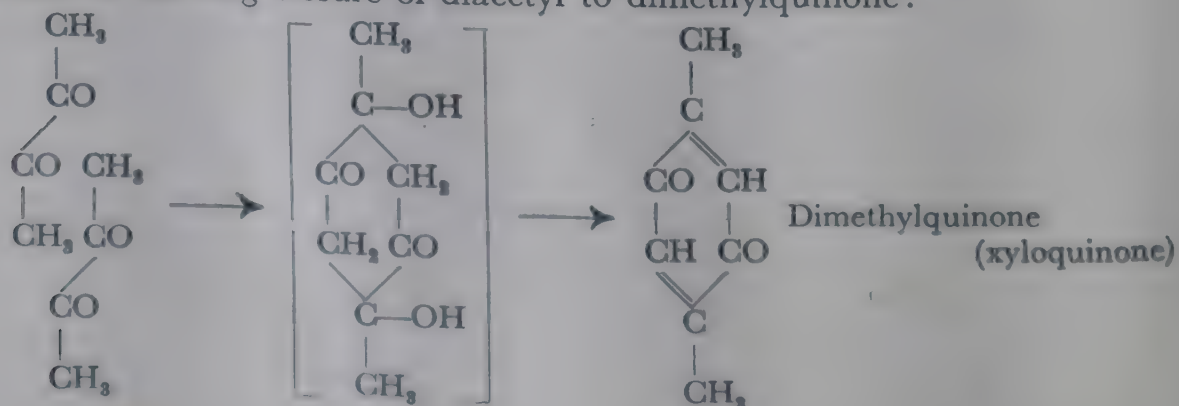
Occurrence and preparation of cyclohexane compounds. The derivatives of *cyclohexane* are very widely spread in nature. The most important monocyclic and bicyclic terpenes and camphors, which will be discussed in some detail further on, belong to this class. Essential oils of plants are rich in them. Polyhydroxycyclohexane compounds (quercitol, inositol, quinic acid), which are related to sugars on the one hand, and to certain tannins on the other, occur very widely in the vegetable kingdom. Finally, many mineral oils contain large quantities of *cyclohexane* compounds.

These natural products are often readily accessible, and are suitable starting products for preparing further *cyclohexane* derivatives. For twenty years the reduction of aromatic substances has been used more and more often for the preparation of hydroaromatic ones. Finally, condensation reactions of aliphatic compounds are often suitable for the synthesis of *cyclohexane* derivatives.

An example of this is the condensation of diethyl succinate to succinosuccinic ester under the action of sodium ethylate:

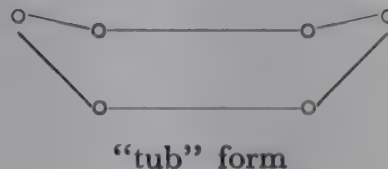
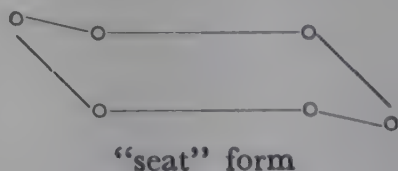


and another is the ring closure of diacetyl to dimethylquinone:



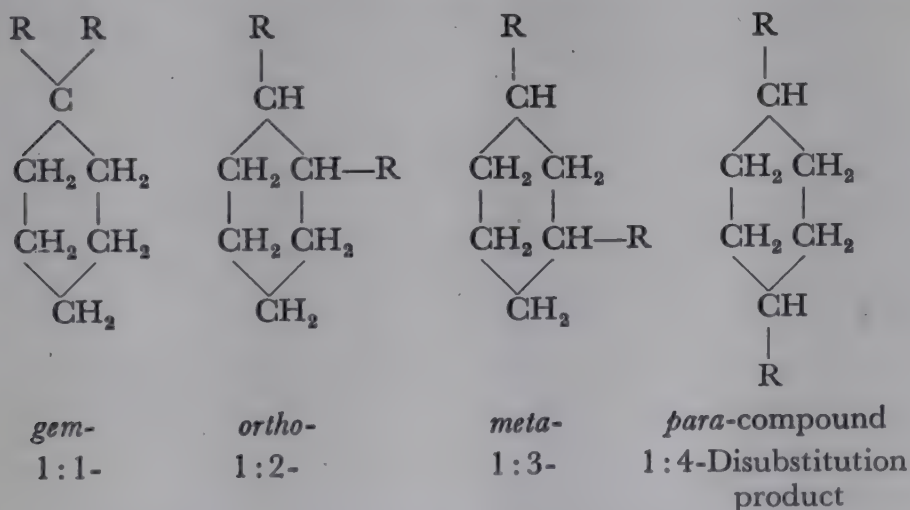
Hydrobenzene derivatives can obviously also be obtained by well-known methods from 1:5- or 1:6-dihalogen compounds, dicarboxylic acids, etc.

Stereoisomerism of cyclohexane compounds. According to the Sachse-Mohr theory *cyclohexane* exists in a "seat" and a "tub" or "boat" form which may be represented from a lateral view as follows:



From electron diffraction spectra, Raman, and infra-red spectra, and also from thermodynamic measurements, it is concluded that at room temperature *cyclohexane* exists mainly in the "seat" form. In the gaseous state the "seat" form passes partly into the "tub" form which contains about 5.6 kcal. per mol more energy. To effect this configurational change it is only necessary for one half of the molecule to move so that the configuration passed intermediately is not uniplanar, but one containing only five C-atoms in one plane whilst the sixth remains in its original place outside the plane ("couch" form). One or the other of these configurations will be stabilized according to the substitution of the *cyclohexane* ring and its derivatives with other ring systems.

The disubstitution products of *cyclohexane* exist in four structural isomerides :



Of these, the 1:1-(*gem*)-derivative exists in only one form.

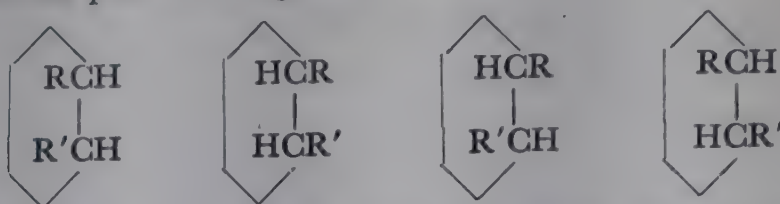
In the case of *ortho*- and *meta*-substitution products theory requires the existence of stereoisomerides as follows:

(a) substituents of the same sort (R, R):

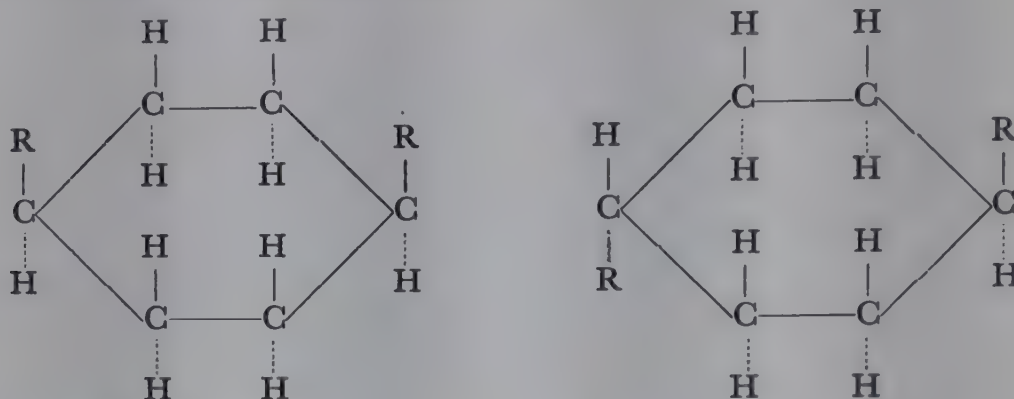
The two substituents can be in the *cis*- or *trans*-positions. The *cis*-forms have a symmetrical structure (internally compensated) and can therefore not be resolved into enantiomorphous forms. The *trans*-compounds are racemic in nature, and can be resolved into optically active components. If, therefore, a *cyclohexane* derivative which has the same substituents in the *ortho*- or in the *meta*-positions, can be obtained in optically active forms, its *trans*-nature is thus unequivocally established. On the other hand, if it cannot be resolved it will be a *cis*-compound.

(b) substituents of different kinds (R, R'):

In this case too, the two substituents may be in the *cis*- or the *trans*-positions with regard to the plane of the *cyclohexane* carbon atoms. Both *cis-trans-isomerides* have two structurally different asymmetric carbon atoms. Hence, two optically active *cis*-compounds (first pair of antipodes), and two optically active *trans*-compounds (second pair of antipodes) are known:

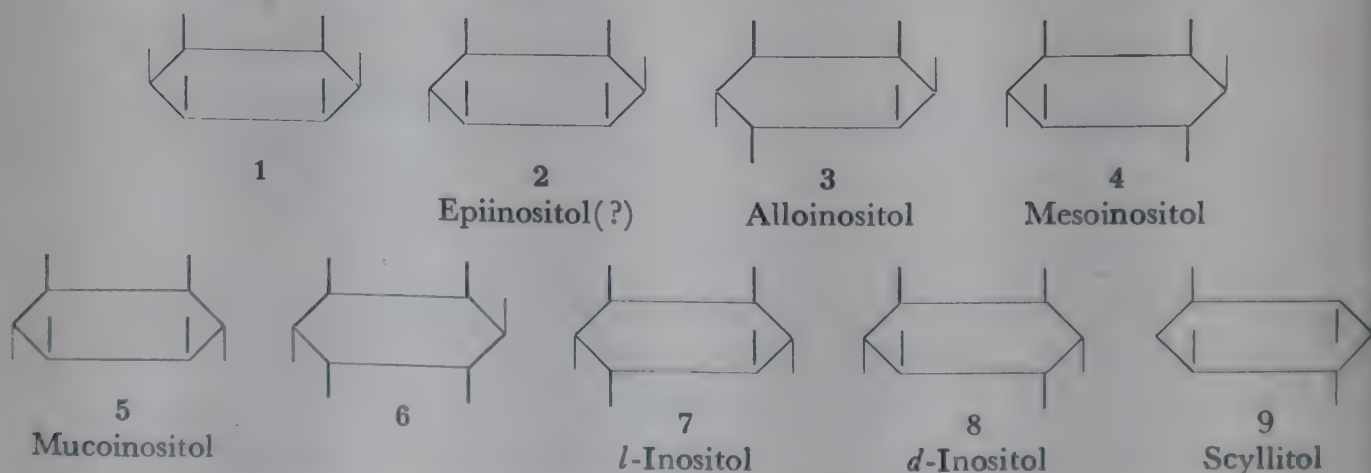


The *para*-disubstitution products of *cyclohexane* must exist in two stereoisomeric forms, whether the substituting groups be the same or different. One may be called the *cis*-form, the other the *trans*:



Both have a plane of symmetry, and are therefore optically inactive.

Amongst the higher-substituted *cyclohexane* compounds, those in which each carbon atom of the *cyclohexane* ring carries one hydrogen atom and one substituent R are of special stereochemical interest. Compounds of this type, namely the 1:2:3:4:5:6-hexahydroxycyclohexanes, are fairly abundant in nature. They are called *inositols*. They can occur in eight *cis-trans-isomerides*, one of which occurs in a *d*- and in a *l*-form; they can be represented schematically as follows (the substituent R is marked by a line):



All these compounds, with the exception of the forms 7 and 8, have a symmetrical structure and are therefore inactive. The latter are mirror-images, and so cannot be superimposed, although they do not contain asymmetric carbon atoms. Their molecules are asymmetric. This is a case of so-called *molecular asymmetry*. In this form, which has identical substituents in the 1-, 2-, and 4-positions on the same side of the carbon plane, each carbon atom is linked by both

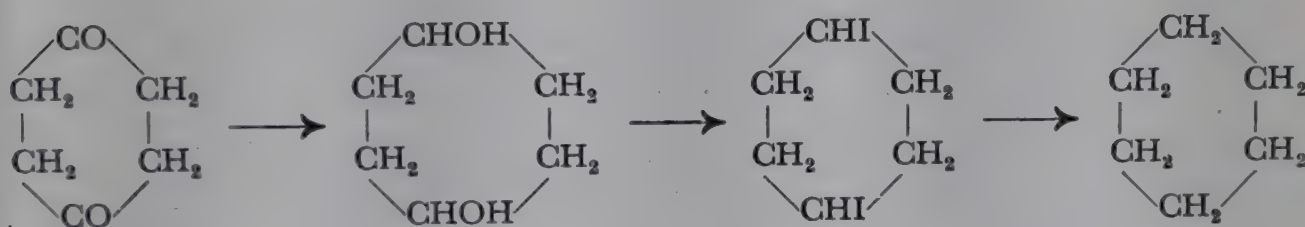
its ring valencies to a radical consisting of two structurally identical, but asymmetrically different halves, i.e. halves which are not related to each other as object and mirror image.

If a hexasubstitution product of *cyclohexane* with six identical substituents attached to the six carbon atoms is optically active, then it must have the configuration 7 or 8. This is the case with *optically active inositol* (see p. 676–77).

Hydrocarbons of the cyclohexane series

A. Saturated hydrocarbons

CYCLOHEXANE. This hydrocarbon occurs in very considerable quantities in Caucasian and Galician mineral oil. It can be obtained synthetically by numerous methods. The older processes, e.g. the reduction of *cyclohexanone* or *cyclohexadione* with hydriodic acid:

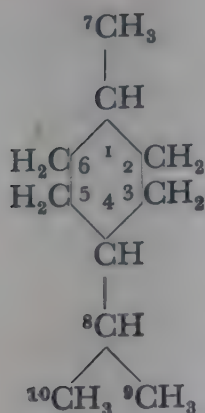


or the decomposition of *cyclohexanecarboxylic acid* by heating with lime, now have only slight importance, since it has become possible to reduce benzene catalytically to *cyclohexane*. The method of Sabatier and Senderens, of reducing with nickel and hydrogen at about 180–250° is particularly suitable, and is carried out on an industrial scale. Benzene, dissolved in glacial acetic acid, may be reduced by hydrogen and platinum black to *cyclohexane* even at room temperature. The success of this reaction depends on the entire exclusion of impurities, particularly also of thiophen.

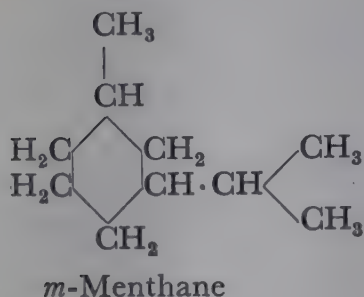
Cyclohexane is a very stable hydrocarbon, boiling at 80°. In the dark it does not react with bromine, but in the light substitution occurs. Under the action of anhydrous aluminium chloride it is converted into higher-boiling products. Potassium permanganate breaks down *cyclohexane* on heating into adipic acid. Fuming sulphuric acid dehydrogenates it even in the cold, the chief product of the reaction being benzenesulphonic acid.

Of the *homologues* of *cyclohexane*, *methylcyclohexane*, (b.p. 103° (760 mm)), and *1:3-dimethylcyclohexane*, deserve mention because of their occurrence in numerous mineral oils. The latter compound can exist in *cis-trans*-isomerides, and the products isolated from petroleum are possibly mixtures of these two forms in varying proportions. B.p. about 118–120°.

1-Methyl-4-isopropylcyclohexane, usually called *p-menthane*, is of importance as the parent substance of important natural terpenes and camphors:



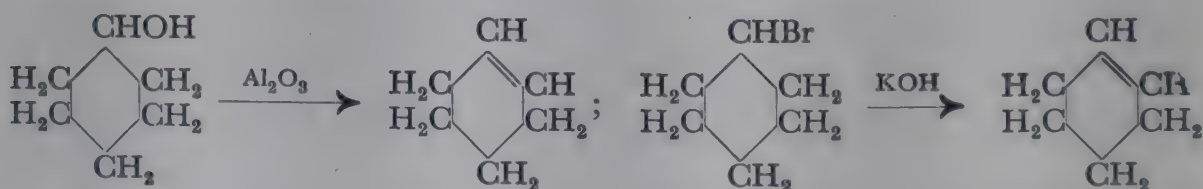
It has been prepared by the hydrogenation of *p*-cymene, limonene (see p. 670), terpinene (see p. 668), and 3-menthene (see p. 667). It boils at 169–170°, and has a fennel-like odour, as well as a somewhat petroleum-like smell. The numbering of the carbon atoms in the *p*-menthane skeleton is shown in the accompanying formula.



1-Methyl-3-isopropylcyclohexane, or *m*-menthane, is also the parent substance of some natural and synthetic terpenes.

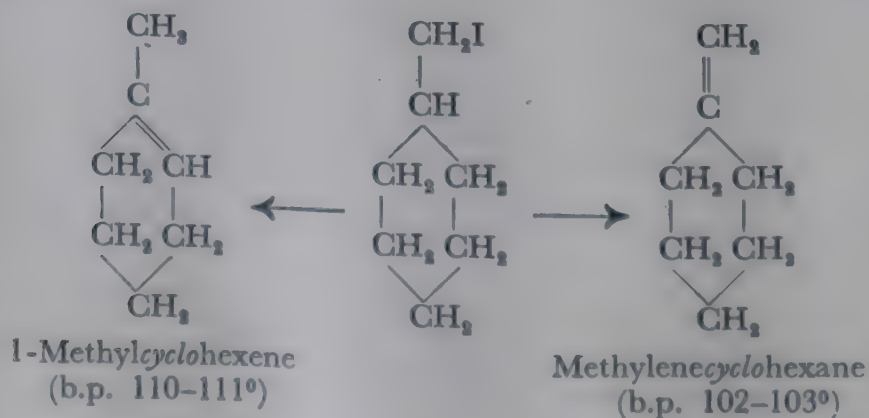
B. Unsaturated hydrocarbons with one double bond

The most convenient method of preparing *cyclohexene* is probably the removal of water from *cyclohexanol*, which may be brought about by passing the latter over heated alumina, or by dehydrating it with potassium bisulphate. *Cyclohexene* may be obtained from monohalogen-substituted *cyclohexane* by eliminating the hydrogen halide by means of quinoline or alcoholic potash:



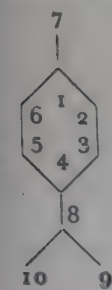
The hydrocarbon boils at 82–83°, is strongly unsaturated, and shows the general properties of an ethylenic compound. The disproportionation of *cyclohexene* to benzene and *cyclohexane* has been referred to on p. 662.

The three isomeric methylcyclohexenes and methylenecyclohexane are also known. Two of them are formed together by the action of quinoline on 1'-iodo-1-methylcyclohexane:



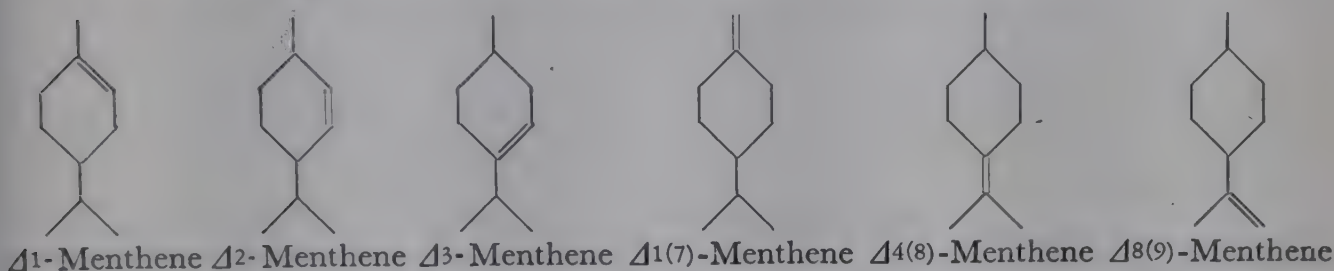
Methylenecyclohexane has a so-called *semicyclic* double bond, i.e. one leading from the ring to the side chain.

Six unsaturated hydrocarbons with *one* double bond are derived from *p*-menthane. In order to indicate unequivocally the position of the double bond in naming the compound, the number of the carbon atom from which the double bond starts is put as an index after the sign Δ , the sign for unsaturation. This proposal is due to Baeyer. If it leads from the nucleus to the side chain or is wholly in the side chain, the end of the double bond is indicated by a number *in parentheses*.



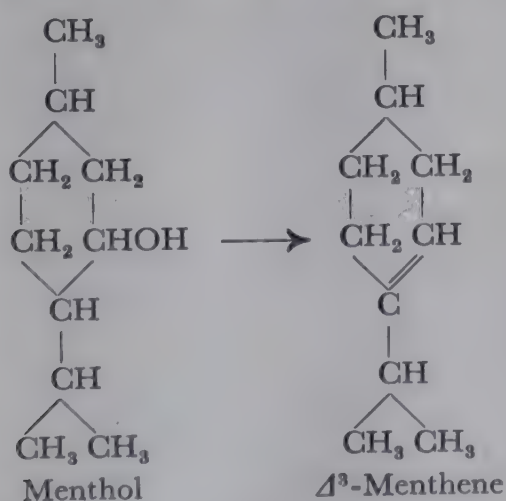
Just as it is customary to represent the formula of benzene by a simple hexagon, in the chemistry of the terpenes and camphors an abbreviated, schematic way of writing the formulæ of the important *p*-menthane and its derivatives has been introduced. It is shown in the accompanying diagram, and will often be used in the sequel.

The following formulæ thus stand for the six possible *menthenes*:

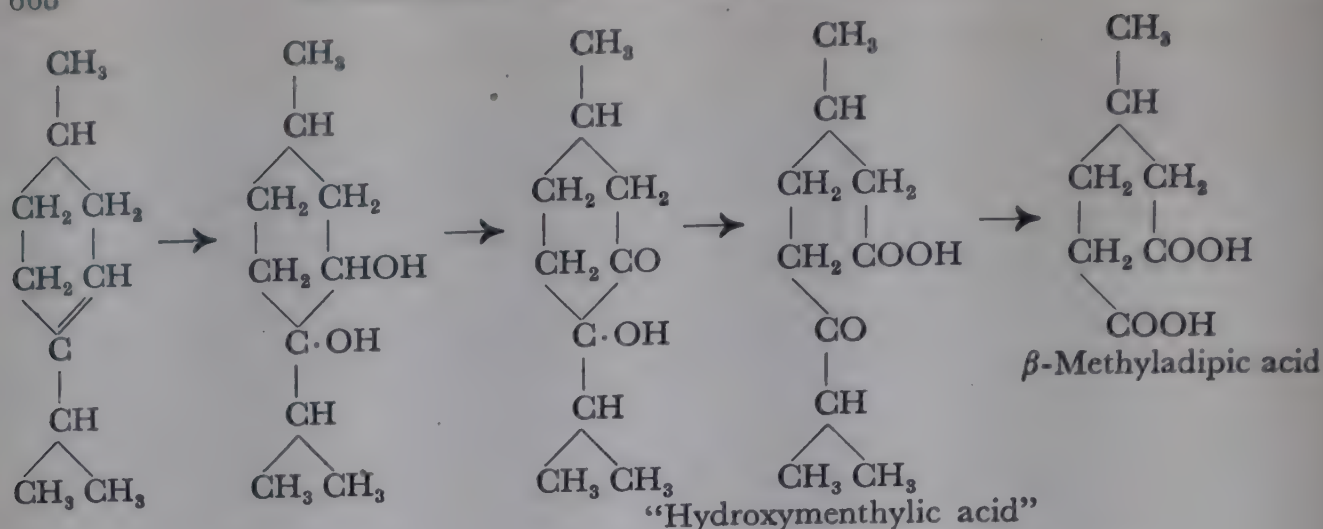


Δ^1 -Menthene is formed from carvomenthol by dehydrating it with potassium bisulphate, Δ^2 -menthene is obtained by the reduction of α -terpinene with sodium and amyl alcohol, and $\Delta^{8(9)}$ -menthene is prepared from isopulegone semicarbazone by heating with sodium ethylate under pressure.

The most important compound of the series is Δ^3 -menthene, often called simply *menthene*, which occurs naturally in thyme oil. It is readily obtained by the elimination of water from menthol (by the xanthate ester method, see p. 51), or by the removal of hydrogen chloride from menthyl chloride:



Δ^3 -*p*-Menthene is known in the inactive and in the two optically forms ($[\alpha]_D = \pm 112.7^\circ$). It boils at 168° , and has an odour similar to cymene. It is oxidized by potassium permanganate through various intermediate products, which can be isolated, to β -methyladipic acid. This degradation proves the constitution of the hydrocarbon:

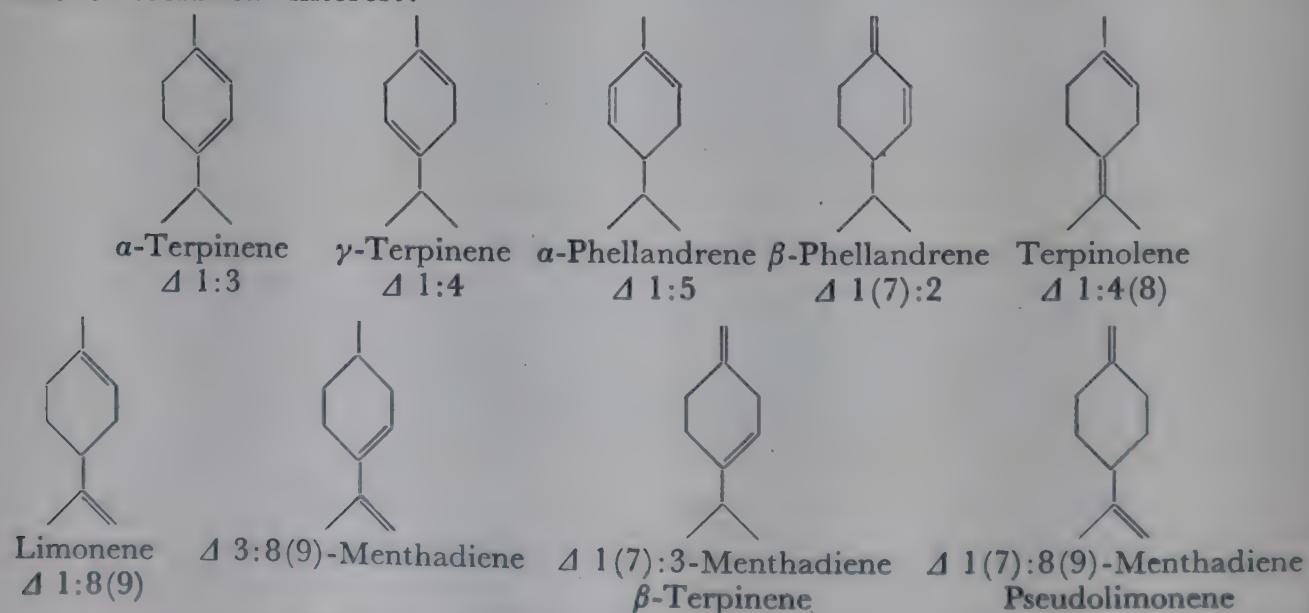


C. Unsaturated hydrocarbons with two double bonds.

The two hydrocarbons, *cyclohexadiene*-(1:3), and *cyclohexadiene*-(1:4) which can also be regarded as dihydrobenzenes, are produced together in various ways that yield mixtures of varying composition, in which, however, *cyclohexadiene*-(1:3) always predominates. The latter is conveniently prepared, for example, from 1:2-dibromocyclohexane by eliminating hydrogen bromide by means of quinoline (or sodium ethylate). It boils at 82–83° (760 mm). *Cyclohexadiene*-(1:4) does not yet appear to have been obtained in a state of purity.

The constitution of the two *cyclohexadienes* can be arrived at by oxidative degradation. In the case of the first compound, succinic acid and oxalic acid must be obtained, and in the second case malonic acid.

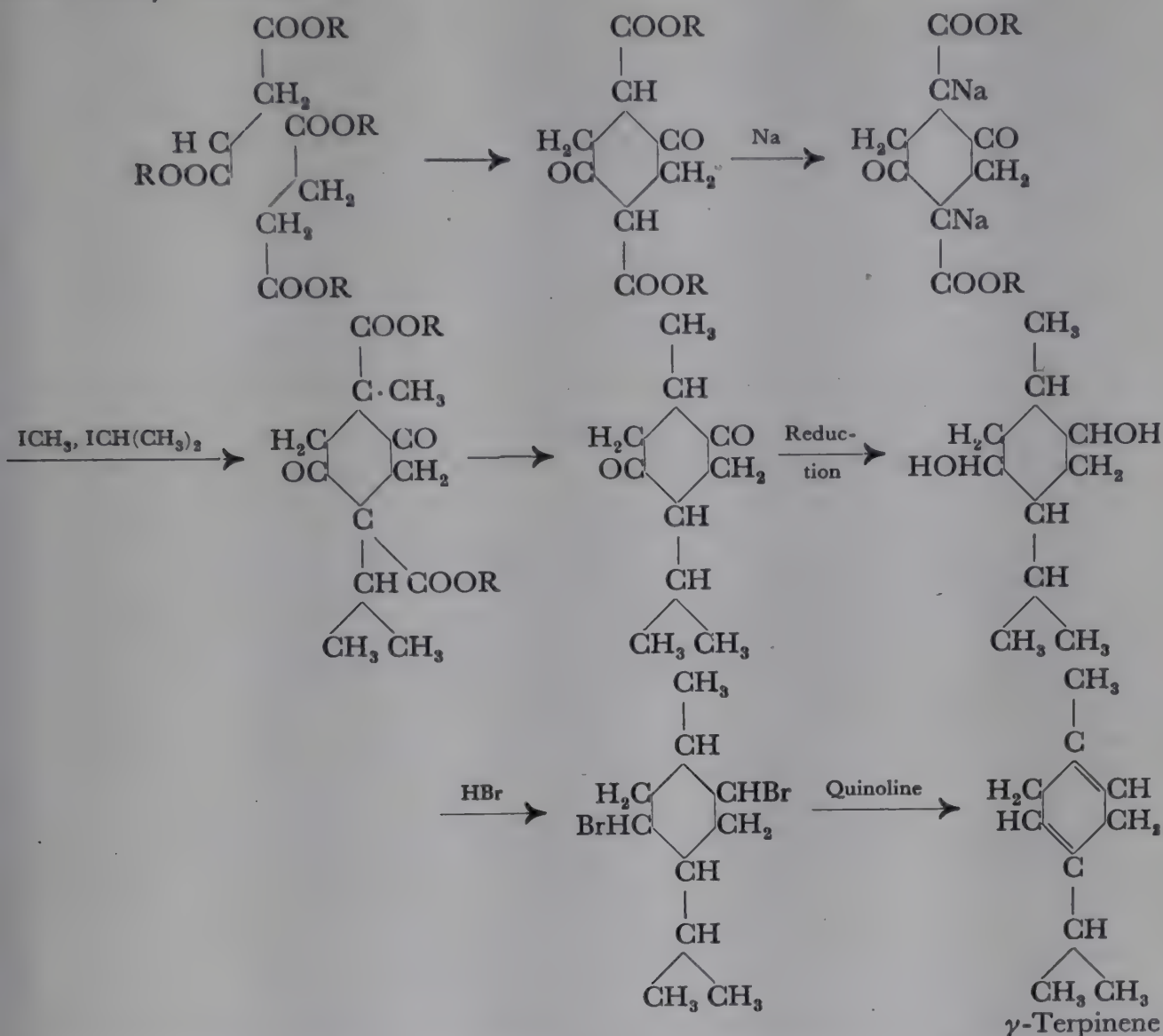
Under the name *menthadienes* is comprised a group of terpenes, of which several representatives are found in very considerable quantities in essential oils of plants. They have, in part, been thoroughly investigated chemically, and are also of technical interest:



α -TERPINENE and γ -TERPINENE (also β -terpinene?) always occur together in many essential oils, e.g. in cardamom oil, coriander oil, Manila elemi oil, etc. They have not yet been completely separated from each other. Their presence is detected by oxidation with potassium permanganate, α -terpinene yielding α,α' -dihydroxy- α -methyl- α' -isopropyladipic acid, and γ -terpinene giving a tetrahydric alcohol, $C_{10}H_{16}(OH)_4$.

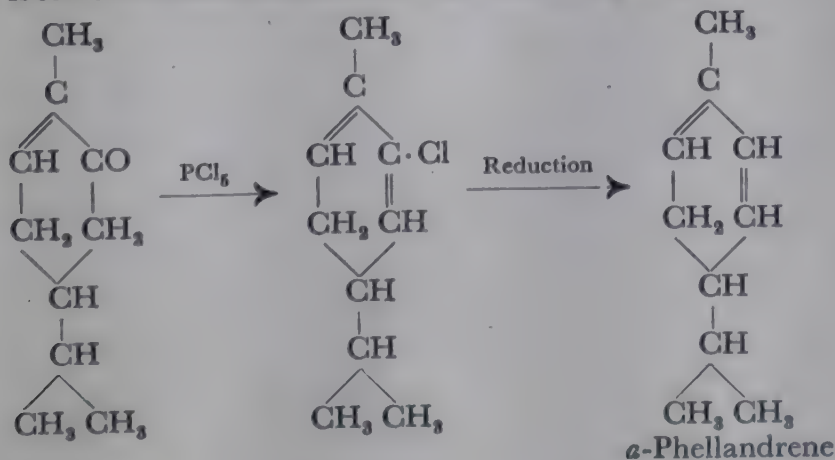
Mixtures of α - and γ -terpinene are obtained synthetically by the action of

acids on various other hydrocarbons (pinene, dipentene, etc.), or on alcohols, such as linalool, terpin hydrate, or terpineol. A synthesis can be carried out starting from diethyl succinate:

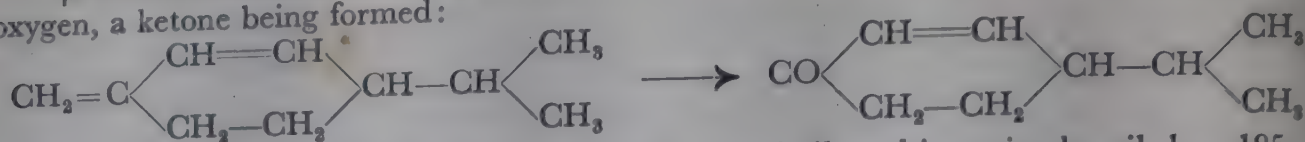


α -PHELLANDRENE is optically active. Its dextrorotatory form is present, e.g. in elemi oil, oil of bitter fennel, and gingergrass oil, and its levorotatory form in eucalyptus oil, Chinese star anise oil, and pimento oil. It appears to be accompanied almost always by smaller amounts of β -phellandrene. Its boiling point is $173\text{--}175^\circ$ (754 mm).

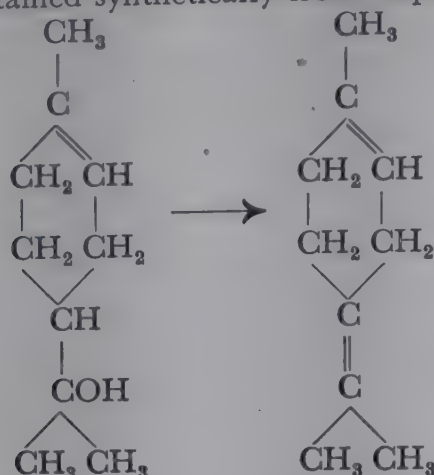
The constitution of α -phellandrene follows, for instance, from the fact that it is converted into Δ^1 -menthene on suitable reduction, and, on the other hand, that it is formed from Δ^6 -menthenone-2 in the following way:



β -PHELLANDRENE contains a semicyclic double bond, which is split by atmospheric oxygen, a ketone being formed:



TERPINOLENE is probably present in Manila elemi oil, and in coriander oil; b.p. 185–187°. It is obtained synthetically from terpineol by removing water with oxalic acid:

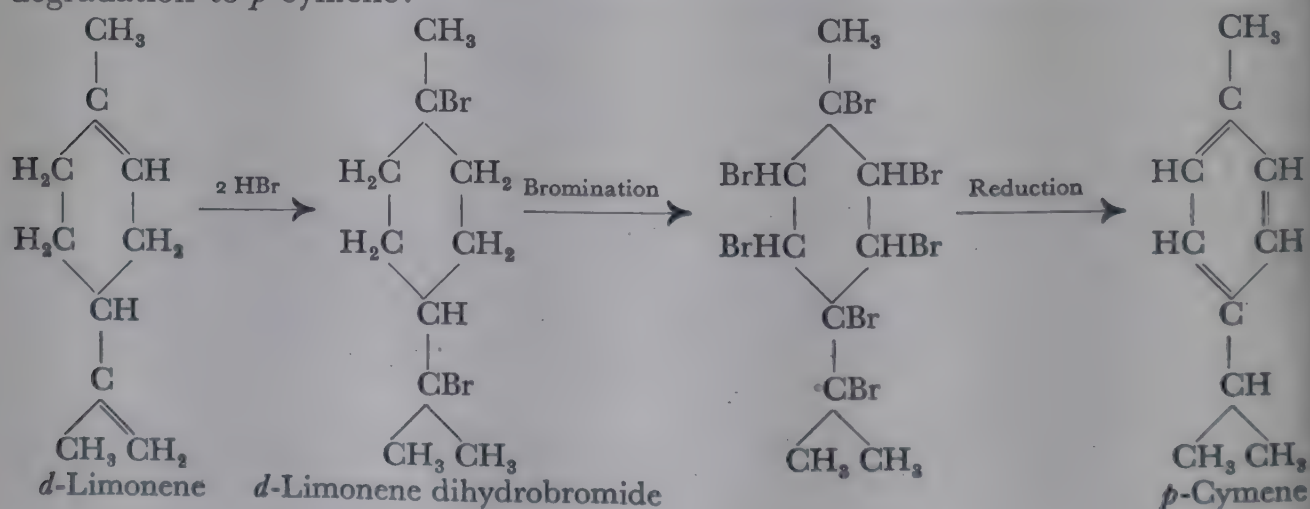


The crystalline tetrabromide (m.p. 116°) serves to characterize the substance.

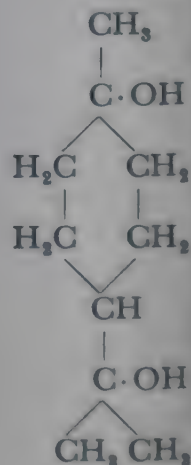
LIMONENE. This hydrocarbon is very abundant in essential oils in the dextro-, lævo-, and inactive forms. *d*-Limonene is found, e.g. in the oil from orange skins, and caraway oil; *l*-limonene is present in the oil of pine needles and fir-cones, whilst the racemate, which bears the name *dipentene*, occurs very abundantly in turpentine oil.

Limonene has an odour like lemons, b.p. 175°, $[\alpha]_D = \pm 125^\circ$ (highest observed value).

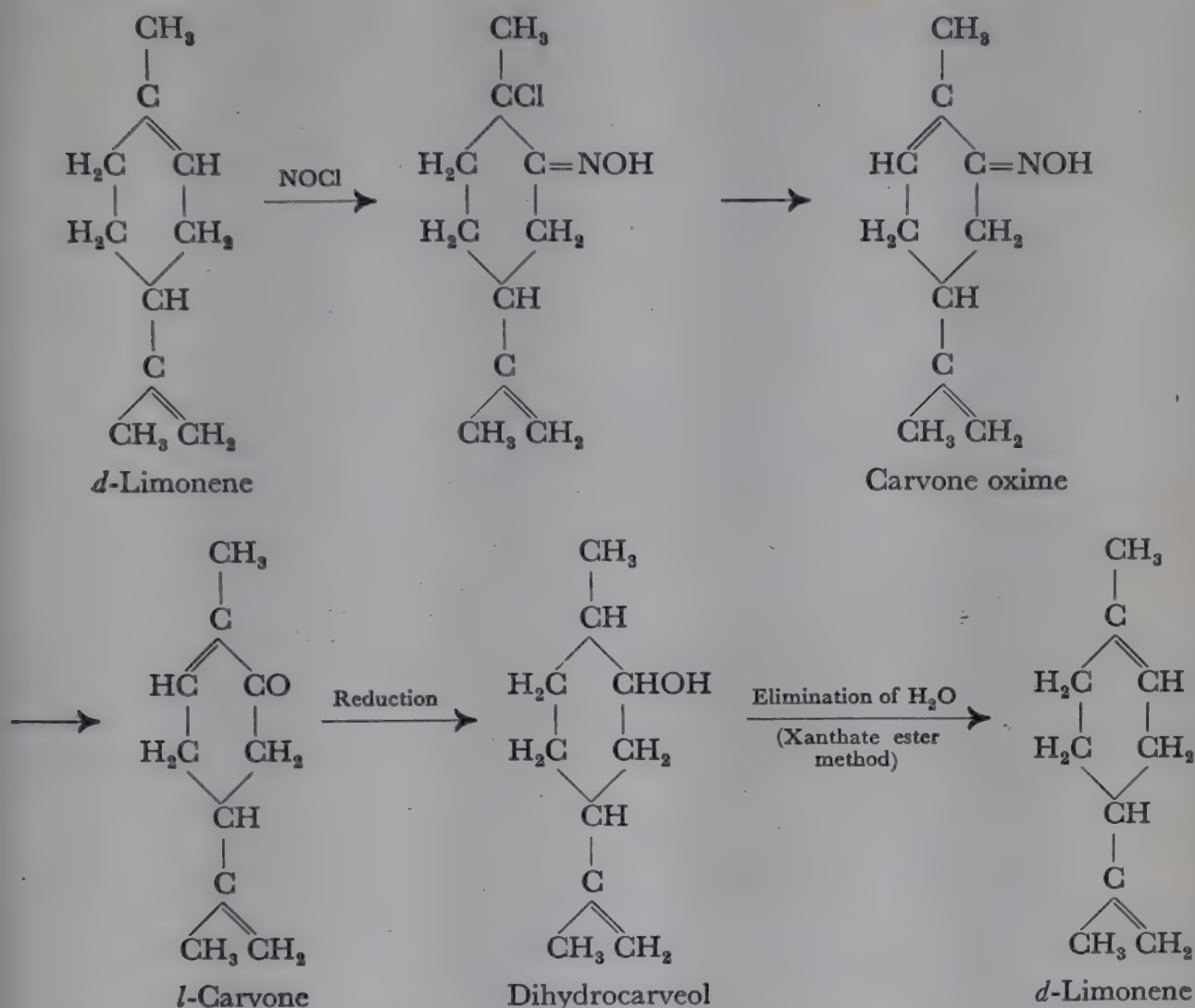
The constitution of the hydrocarbon is arrived at on the one hand from its degradation to *p*-cymene:



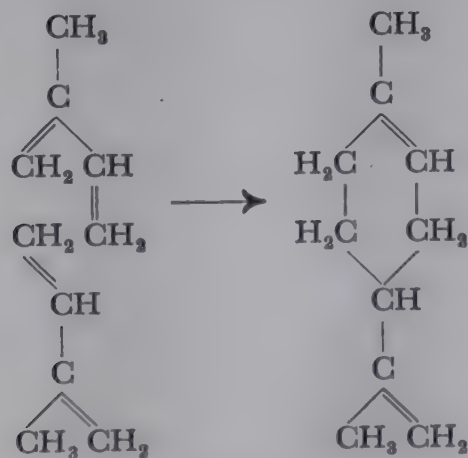
and on the other hand from the fact that 1:8-dibromomenthane (limonene dihydrobromide) which is obtained by the addition of hydrogen bromide to limonene, is identical with the product obtained by the action of hydrogen bromide on 1:8-terpin:



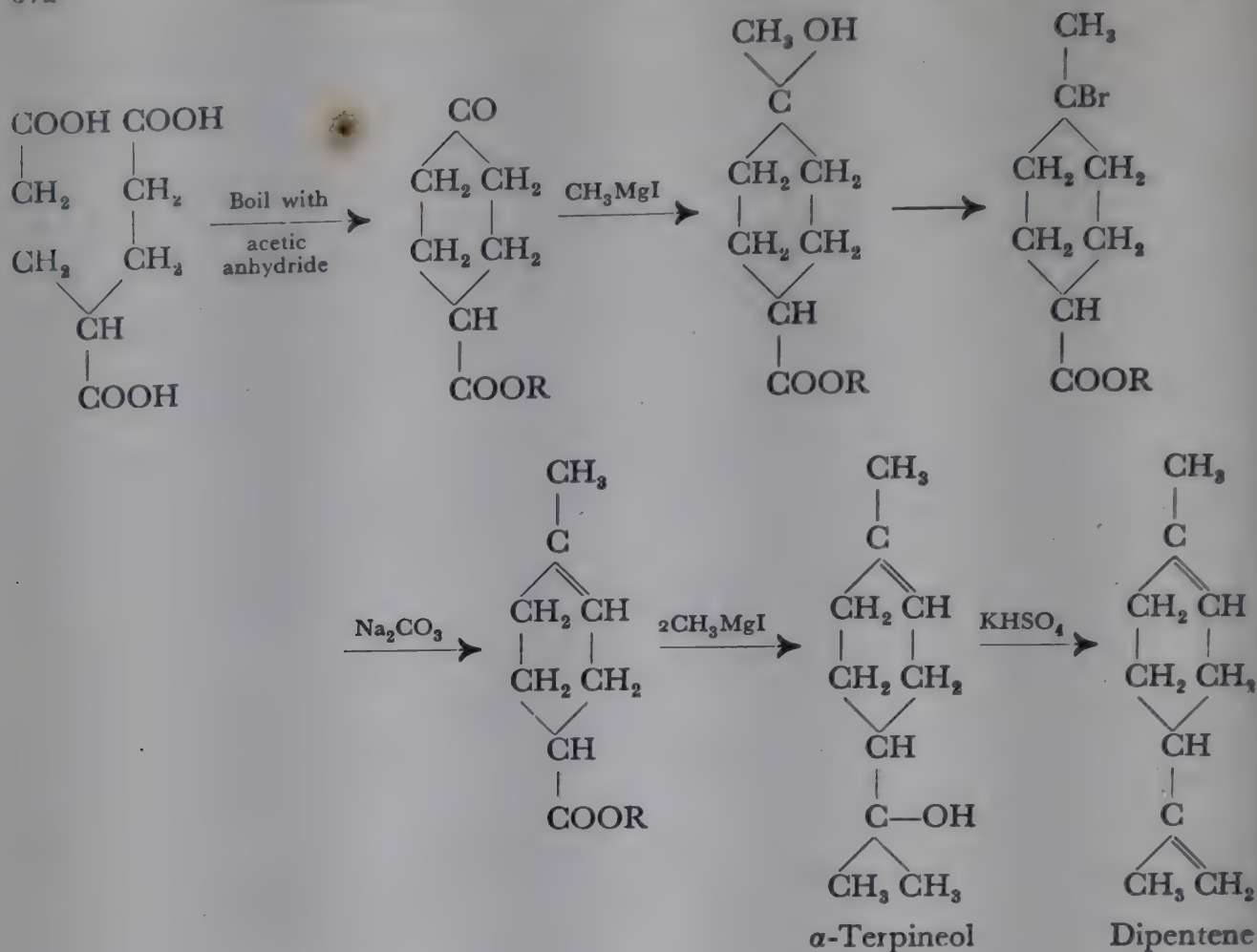
and also from the relationship between limonene and carvone, into which it can be converted, and from which it can be obtained through dihydrocarveol (H. Goldschmidt):



Inactive limonene, *dipentene*, has been synthesized in several ways. It is formed by a polymerization process, together with other products, on heating isoprene to about 300° :



It is also formed by removal of water from terpin hydrate (see p. 681) and α -terpineol with potassium bisulphate, and finally by a beautiful synthesis due to W. H. Perkin, jr., which at the same time is also one for inactive α -terpineol. It starts from γ -carboxylated pimelic acid:

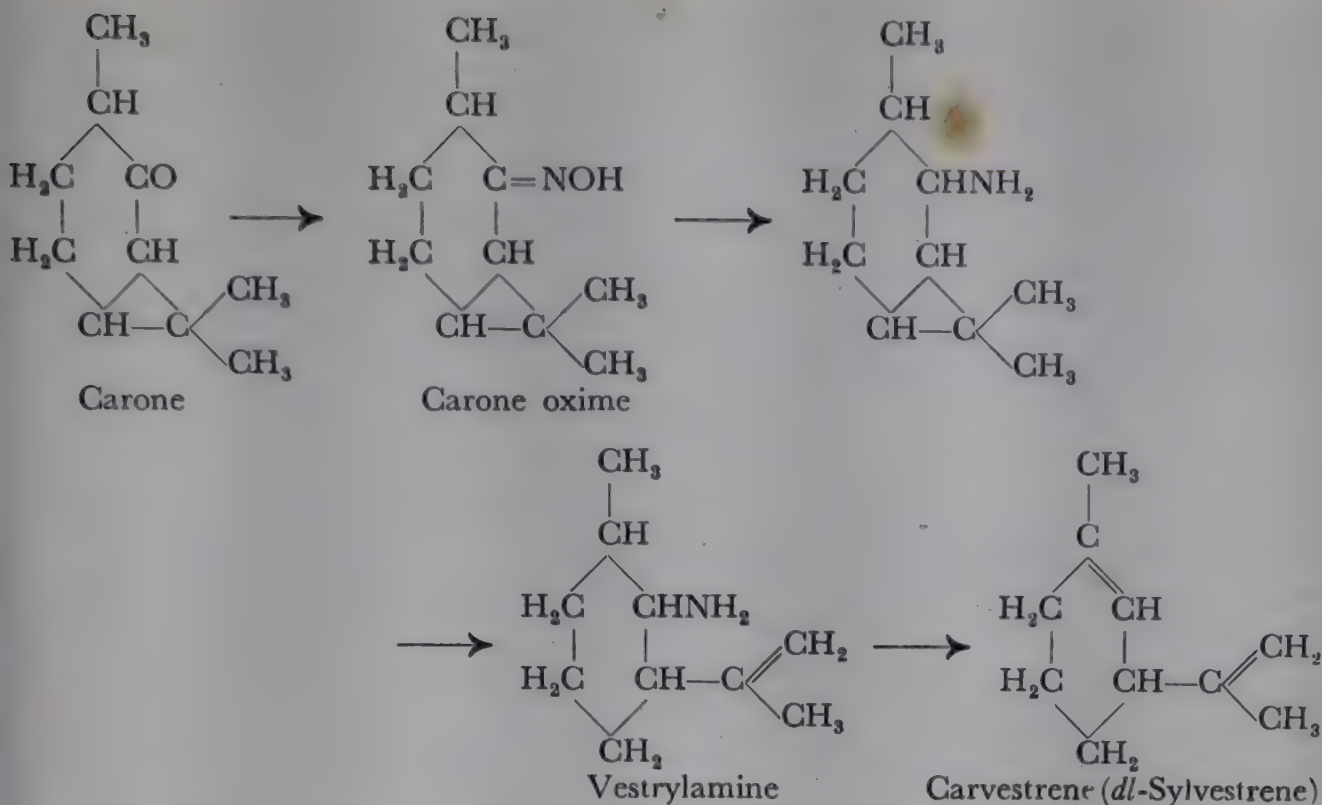


Very pure dipentene is also obtained by the dry distillation of rubber. The tetrabromides of the limonenes and dipentene, which crystallize well, are suitable for characterizing these substances. Those from the limonenes melt at 104.5° and are optically active. Dipentene tetrabromide melts at 125° .

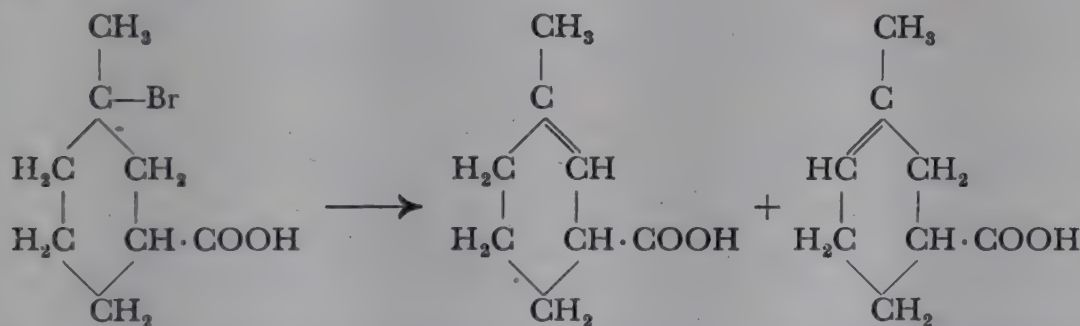
SYLVESTRENE. This hydrocarbon is contained in the dextrorotatory form in some pine oils and turpentine oils, but is rather rare. Possibly it is formed in some cases only during the process of isolation from natural turpentine oil. Thus, Simonsen demonstrated, for example, the presence of a hydrocarbon, *d*-carene, in Indian turpentine oil, which gives sylvestrene when acted upon by hydrogen chloride. Sylvestrene is very similar to limonene in its physical and chemical properties. In its constitution it only differs from limonene in being a derivative of *m*-menthane. Sylvestrene boils at $175\text{--}176^\circ$, and has a specific rotation $[\alpha]_D +66.3^\circ$ in chloroform.

The constitution of sylvestrene is supported by its degradation to *m*-cymene, and by two syntheses by which the hydrocarbon has been obtained in the racemic and in optically active forms.

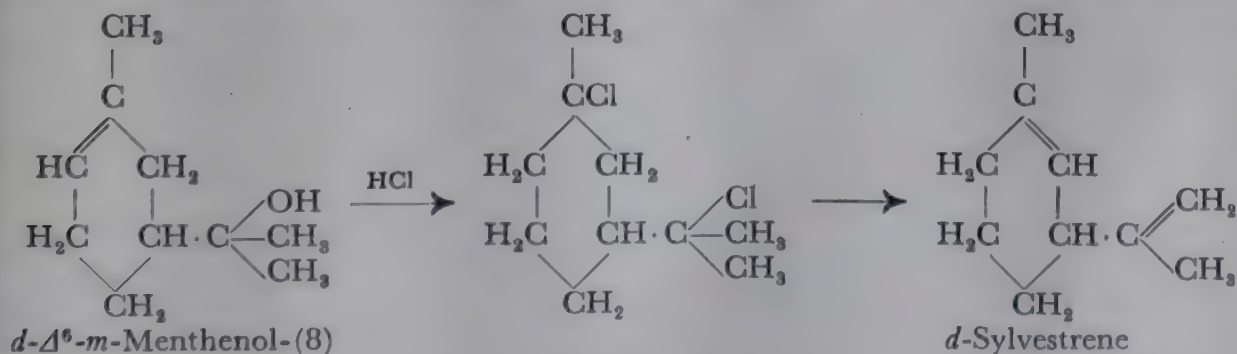
The first synthesis is due to Baeyer. It starts with carone (see p. 695). This is converted into its oxime, and the latter into the corresponding amine by reduction. When the amine is warmed with acid, the three-membered ring is ruptured. The compound formed, *vestrylamine*, gives inactive sylvestrene on dry distillation of its hydrochloride, ammonium chloride being split off. Inactive sylvestrene is also called *carvestrene*.



The synthesis of optically active sylvestrene has been accomplished by Haworth and Perkin. Starting with 1-bromo-1-methylcyclohexane-3-carboxylic acid they obtained a mixture of the Δ^1 - and Δ^6 -unsaturated acids by splitting off hydrogen bromide:



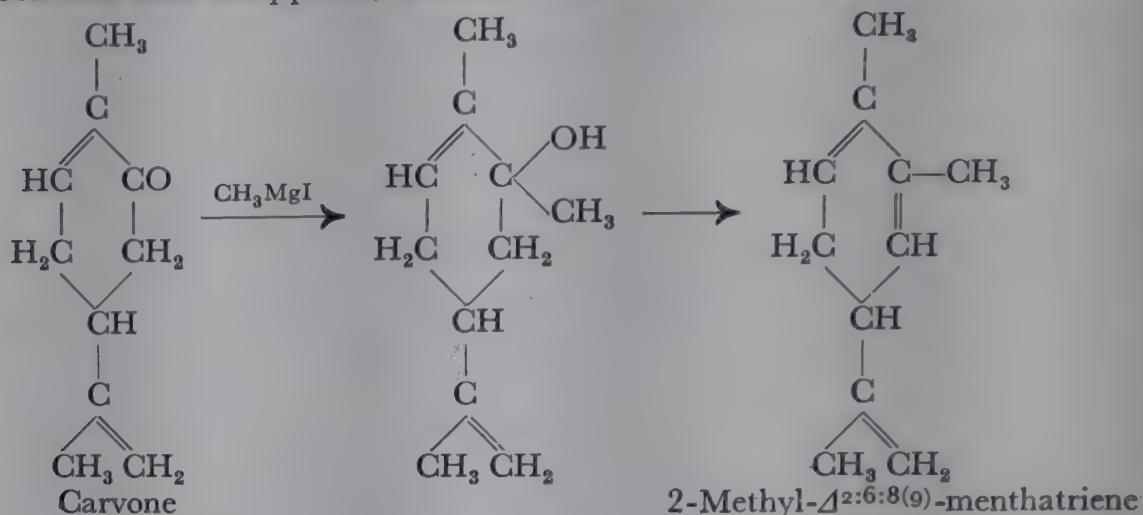
The latter was resolved by means of the brucine salt, and after esterification, was treated with methylmagnesium salt. *d*- Δ^6 -*m*-Menthenol-(8) was thus formed, which was converted into *d*-sylvestrene dihydrochloride. By removal of hydrogen chloride a product was obtained which was identical with natural sylvestrene:



Cyclohexatriene. As explained before, the benzene compounds, which have a special, relatively saturated nature, fall into this group.

An interesting menthatriene derivative, which has only two double bonds in the ring, and one in the side chain, has been synthesized by Klages and Ruge

Methylmagnesium salt was added to optically active carvone, and water was removed from the alcohol formed. The 2-methyl- $\Delta^{2:6:8(9)}$ -menthatriene so obtained is an optically active, very unstable hydrocarbon, which readily adds on bromine, and instantly decolorizes potassium permanganate. On heating with a three per cent solution of hydrogen chloride in glacial acetic acid it isomerizes to a benzene derivative, 2-methylcymene. With this rearrangement, accompanied by the migration of the third double bond into the ring, the olefinic nature of the hydrocarbon also disappears, and the substance becomes aromatic.



Alcohols of the cyclohexane series

Hydroxyl derivatives of cyclohexane.

CYCLOHEXANOL, $\text{HOHC} \begin{array}{c} \text{CH}_2-\text{CH}_2 \\ \text{CH}_2-\text{CH}_2 \end{array} \text{CH}_2$. This alcohol has recently

become a readily accessible, and a technically manufactured product, since phenol can be smoothly converted into *cyclohexanol* by catalytic hydrogenation with hydrogen and nickel at 160–170°. In addition, small quantities of *cyclohexanone* are also formed. *Cyclohexanol* can be quantitatively converted into *cyclohexanone* by oxidation, e.g. with chromic acid.

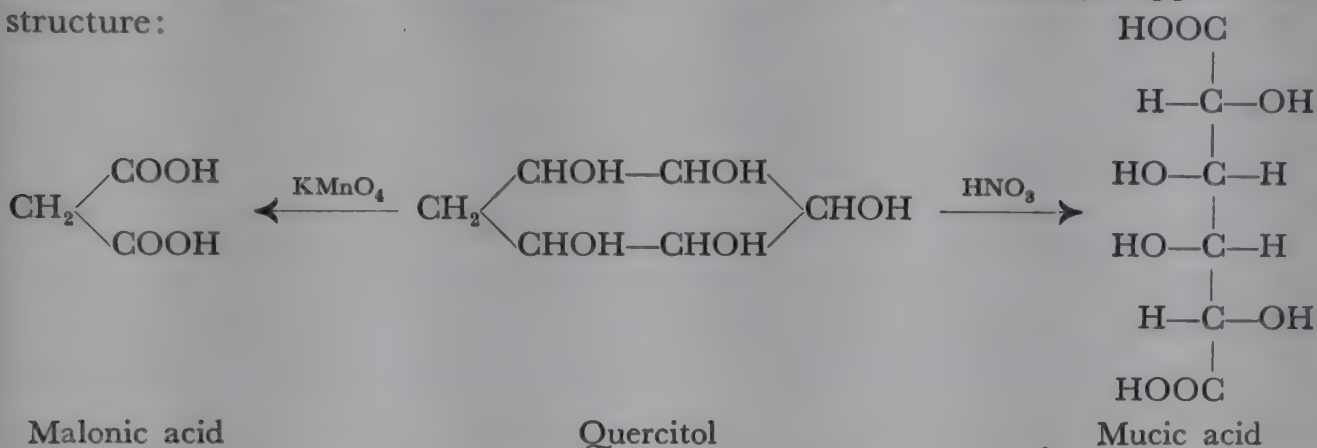
The odour of *cyclohexanol* resembles that of camphor, and it boils at 161°. *Cyclohexanol* acetate recalls amyl acetate in its properties.

CYCLOHEXANEDIOLS. All three position-isomeric dihydroxycyclohexanes are known. They are prepared by hydrogenation of the corresponding dihydric phenols. The longest known and most thoroughly investigated of the three compounds is *cyclohexane-1:4-diol*, called *quinitol*. It exists in two *cis-trans* isomeric forms, of which one (*cis-quinitol*) melts at 100–102°, and the other (*trans-quinitol*) at 139°. They taste sweet. The name *quinitol* expresses the fact that, on the one hand, the compounds are related to the polyhydroxycyclohexanes (*quercitol*, *inositol*) and, on the other hand, to *quinone*, into which it can be converted by oxidation.

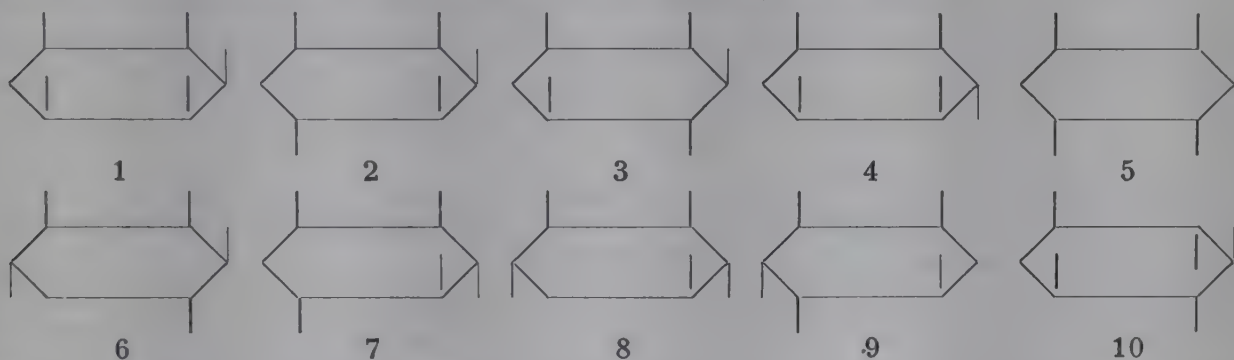
Cyclohexane-1:2:3-triol has been prepared in three isomeric forms (all that are theoretically possible) by the catalytic reduction of *pyrogallol*, and in other ways. The three forms melt at 108°, 124°, and 148°, respectively. *Cyclohexane-1:3:5-triol*, or *phloroglucitol* (m.p. 184°), is obtained by reduction of *phloroglucinol* with sodium amalgam.

QUERCITOL, $C_6H_{12}O_5$, is found in nature in acorns ("acorn sugar"). It contains five alcoholic hydroxyl groups (pentaacetate, pentanitate). Its cyclic nature follows from its close relationship with aromatic substances. On heating *in vacuo* it gives hydroquinone, quinone, and pyrogallol. Hydriodic acid reduces it to benzene, phenol, pyrogallol, quinone, and hexane.

Quercitol must therefore be regarded as a pentahydroxycyclohexane. Its oxidative degradation with nitric acid to mucic acid (and a trihydroxyglutaric acid), and with potassium permanganate to malonic acid (Kiliani), support this structure:



The configuration of mucic acid is known, and as it is an oxidation product of quercitol, the configuration of the latter is also determined. There are ten possible stereoisomeric formulæ for pentahydroxycyclohexane:



(The positions of the five OH-groups are indicated by vertical lines).

Optically active quercitol ($[\alpha]_D = +24.1^\circ$) cannot be numbers 1, 4, 6, or 10 as these are symmetrical. Of the remainder only 8 and 9 contain four hydroxyl groups in the same mutual positions in space as in mucic acid, the oxidation product of quercitol.

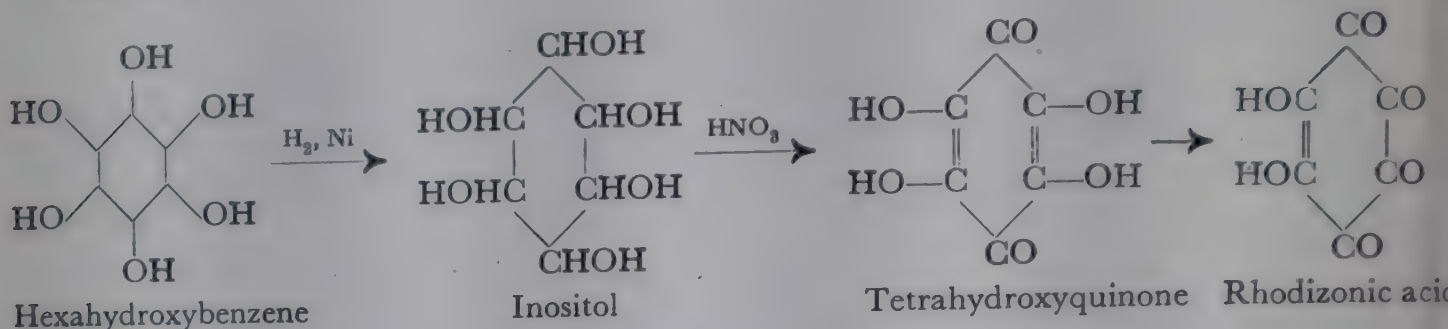
One of them, therefore, represents optically active quercitol. It has been shown that formula 8 represents *l*-quercitol. Both formulæ 8 and 9 agree in the configuration of their asymmetric carbon atoms with active inositol (see below), from which quercitol differs only in having one hydroxyl group less.

Quercitol melts at 234° , and tastes sweet.

INOSITOL. Inactive, or mesoinositol occurs in muscle and in many organs of the animal and human organism. In plants it is also extremely abundant, partly in the free state, and partly esterified with phosphoric acid as *phytic acid*. The latter has also been found in the erythrocytes of hens and other birds. Inositol is a necessary growth-factor for yeast and various other micro-organisms. In some animals too (mice, rats) it has been shown that lack of inositol leads to deficiency diseases.

Inositol forms a hexaacetate. It is hexahydroxy-hexahydrobenzene, since on oxidation with nitric acid it yields tetrahydroxyquinone and rhodizonic acid

(Maquenne). On the other hand, it is formed from hexahydroxybenzene on catalytic reduction with Raney nickel and hydrogen (125–150°); by-products of this hydrogenation are the isomers scyllitol and a new cyclitol which melts at 213–214°:



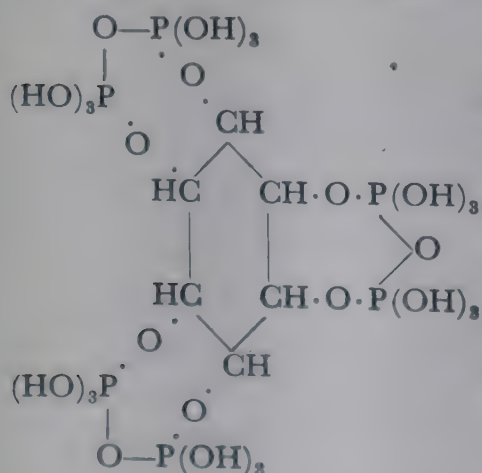
Mesoinositol melts, when anhydrous, at 225°. It is an effective growth-promoting substance, for example, for yeast, and is therefore sometimes also called bios I. A monomethyl ether, *bornesitol*, is found in caoutchouc from Borneo; a dimethyl ether, *dambonitol*, can be isolated from a variety of caoutchouc from Gaboon.

As shown on p. 664, a compound of the type of inositol can exist in 8 *cis-trans* isomerides, of which, however, only one form is racemic, i.e. consists of optically active isomerides.

Methyl ethers of optically active inositol are found in nature.

One of these monomethyl ethers is *pinitol* from *Pinus Lambertiana*. On cleavage with hydriodic acid it gives *d*-inositol. *Quebrachitol* from quebracho bark (and some other plants) is another methyl ether of inositol, giving on hydrolysis *l*-inositol and methyl alcohol.

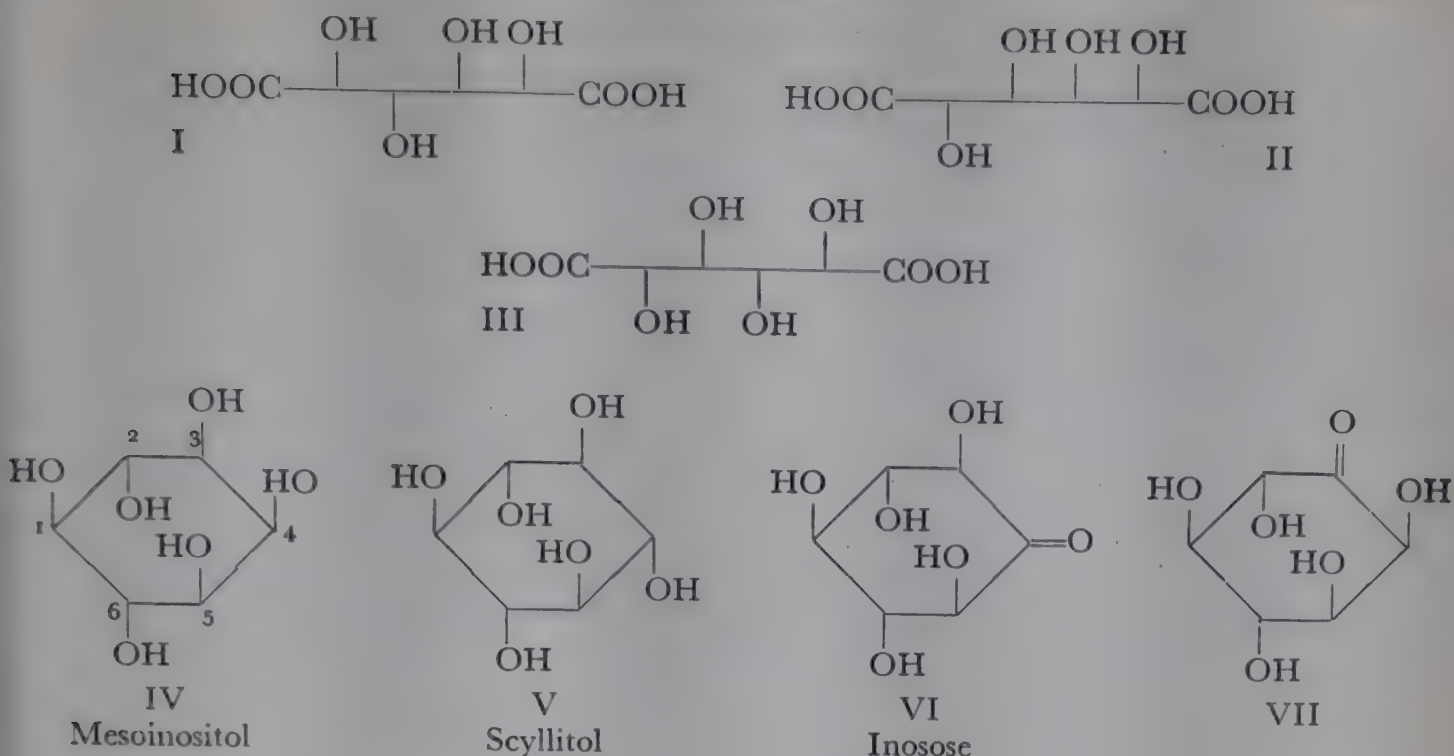
An inactive inositol, different from mesoinositol, is *scyllitol*, which is found, for example, in the cartilage of rays and sharks.



The calcium, magnesium, and potassium salts of a hexaphosphate of mesoinositol occur widely, and in considerable quantities, in plants. They are salts of *phytic acid*, to which the accompanying formula is ascribed. The latter has also been synthesized from inositol, phosphoric acid, and phosphorus pentoxide.

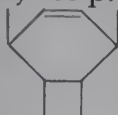
The calcium-magnesium salt of inositol hexaphosphate is used in medicine under the name "phytin".

The configuration of mesoinositol has been made clear by a series of degradation reactions (Th. Posternak). By direct oxidation, DL-saccharic acid (I) and DL-talomucic acid (II) have been isolated from it. The bacterium *Acetobacter suboxydans* oxidizes mesoinositol to a ketose, known as Kluyver's inosose. When oxidized by potassium permanganate the latter gave DL-idosaccharic acid (III). The configuration of mesoinositol is proved to be that of formula IV by the fact that these three dicarboxylic acids are obtained on degradation. Thus, the spatial positions of the hydroxyl groups 1, 2, 3, 4 are evident from the configuration of saccharic acid (I), the positions of the hydroxyl groups 2, 3, 4, 5 from that of talomucic acid (II), and the configuration of the hydroxyl groups 3, 2, 1, 6 from that of idosaccharic acid (III):



Kluyver's inosose is probably represented by formula VI. Formula VII, which might also have been possible, is excluded because it would not yield scyllitol on reduction, but would give *dl*-inositol (besides mesoinositol). As the inosose (formula VI) gives *scyllitol* and mesoinositol on reduction, scyllitol must have formula V.

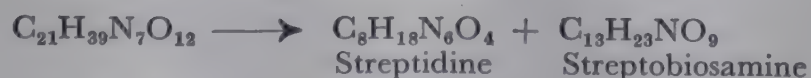
Alloinositol and *mucoinositol* (for formulæ, see p. 664) have been obtained synthetically from a tetrahydroxycyclohexene, conduritol



By the action even of weak bases or sodium acetate the inososes are converted smoothly into 1:2:3:5-tetrahydroxybenzene, which gives phloroglucinol on reduction with sodium amalgam. Probably, a change of inositols into aromatic substances (phenols) *in vivo* is possible; thus, it has been found that a micro-organism (*Pseudomonas Beijerinckii* Hof), growing on salted beans, produces a red pigment, the calcium salt of tetrahydroxyquinone, which has probably been formed from inositol.

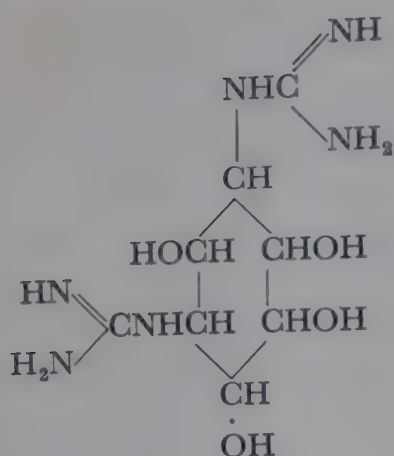
STREPTOMYCIN. This substance, occurring in the micro-organism *Streptomyces griseus*, has recently aroused great interest since it is an excellent antibiotic and is used in medicine against infectious diseases (due to streptococci, staphylococci, coli, and certain forms of tuberculosis).

Streptomycin has the empirical formula $\text{C}_{21}\text{H}_{39}\text{N}_7\text{O}_{12}$. By acid hydrolysis it is split into two components, *streptidine* and *streptobiosamine*:

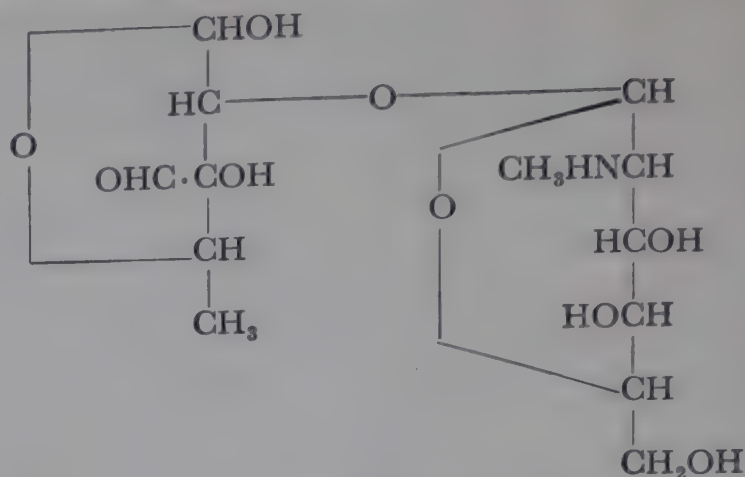


The elucidation of the structure of streptidine has shown it to be a 1:3-diguanidino-2:4:5:6-tetrahydroxycyclohexane; streptomycin is therefore described here, following the inositols. The optical inactivity of streptidine suggests that it is a *meso*-form.

Streptobiosamine is a peculiar disaccharide, being composed of 1-N-methylglucosamine and a methylpentose-like sugar, which, however, contains two aldehydic groups:

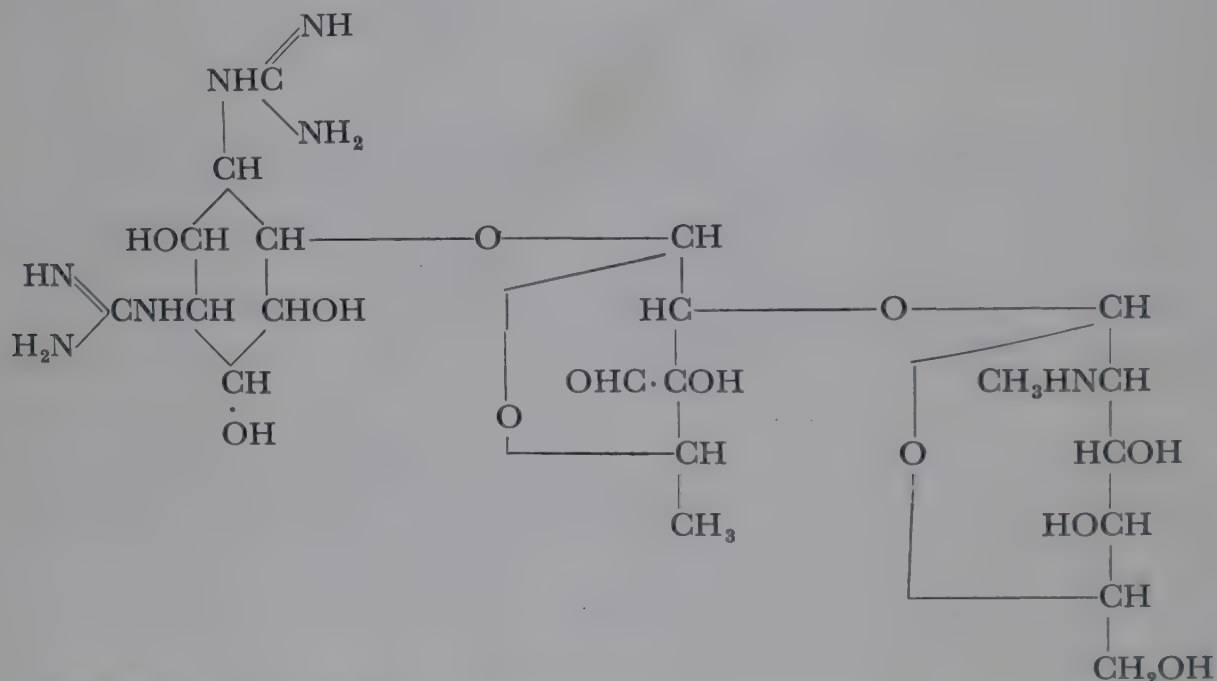


Streptidine



Streptobiosamine

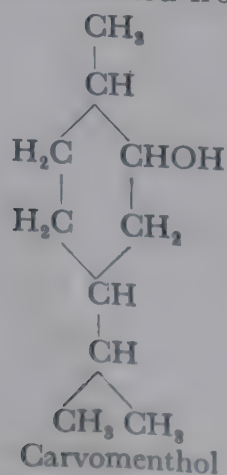
These two fission products, whose constitutions have been proved conclusively by numerous degradation reactions, lead to the following probable structure for streptomycin (K. Folkers and co-workers):



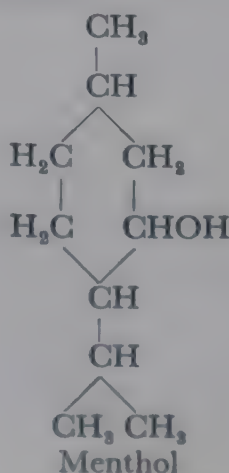
Alcohols derived from *p*-menthane.

Of the *saturated* hydroxy-derivatives of *p*-menthane the following must be mentioned:

Carvomenthol, which is obtained by the complete reduction of carvone (see p. 685), and *menthol*, an important alcohol, which is found in large quantities in peppermint oil, and is obtained from that source:



Carvomenthol

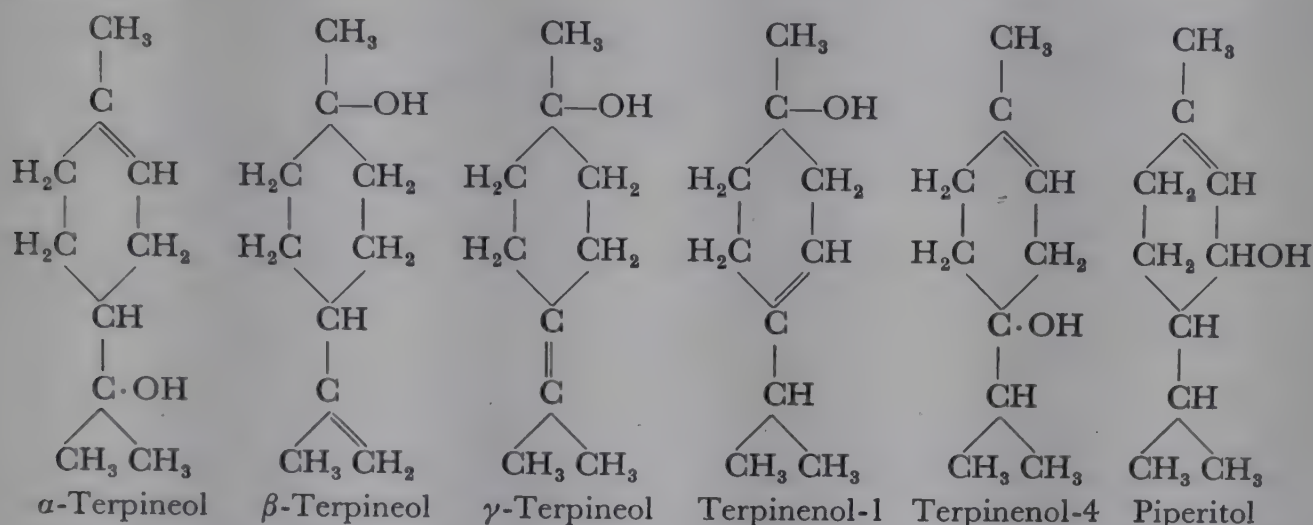


Menthol

The menthol of peppermint oil is laevorotatory ($[\alpha]_D = -49.7^\circ$, without solvent), and boils at $215-216^\circ$. It exists in several crystalline forms, of which only the one melting at 42.5° is stable. Menthol has been obtained synthetically, e.g. by reduction of thymol, and has been resolved as the brucine salt of the acid menthyl phthalate. The three asymmetric carbon atoms in menthol allow the existence of 8 stereoisomeric menthols, of which five are known (*d*- and *l*-menthol, *d*- and *l*-neomenthol, m.p. -22° , and *d*-neoisomenthol, m.p. -8°). In menthol and neomenthol, the methyl and isopropyl groups are in the *trans*-position; in menthol, the hydroxyl is in the *cis*-position, and in neomenthol in the *trans*-position with respect to the methyl group.

Dehydration of menthol gives Δ^3 -menthene.

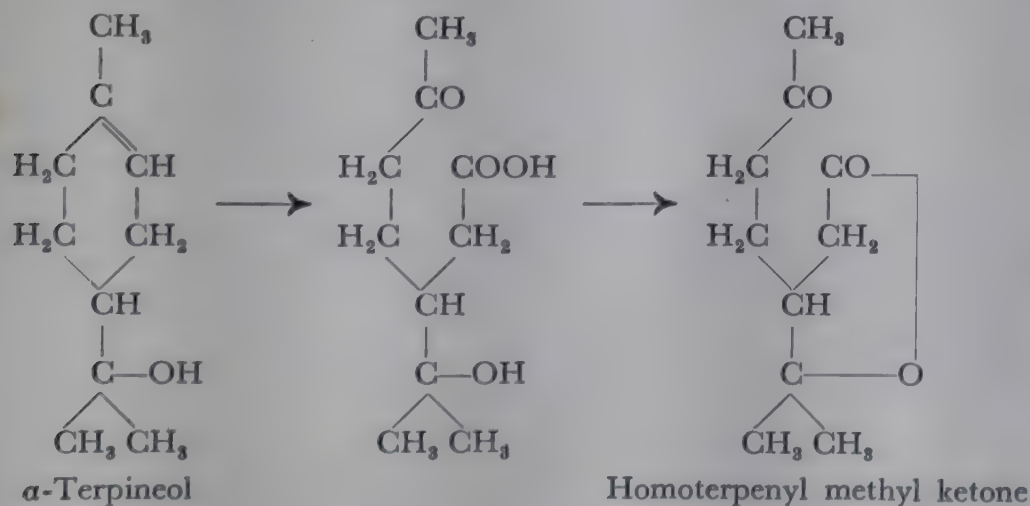
Of the unsaturated alcohols of the *p*-menthane series the following may be mentioned:

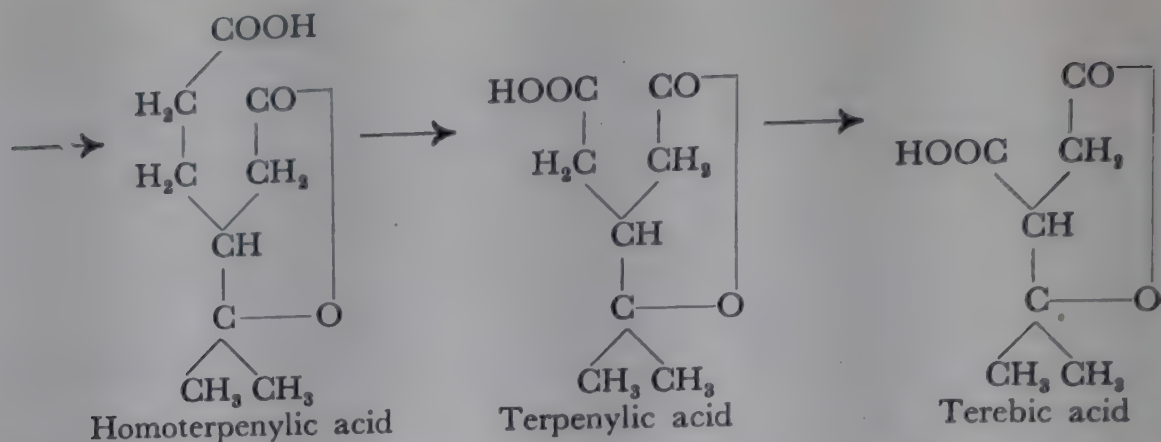


α -Terpineol is found in nature in numerous essential oils, such as cardamom oil, cajuput oil, and oil of marjoram, and *terpinenol-4* in oil of juniper berries, cardamom oil, nutmeg oil, etc.

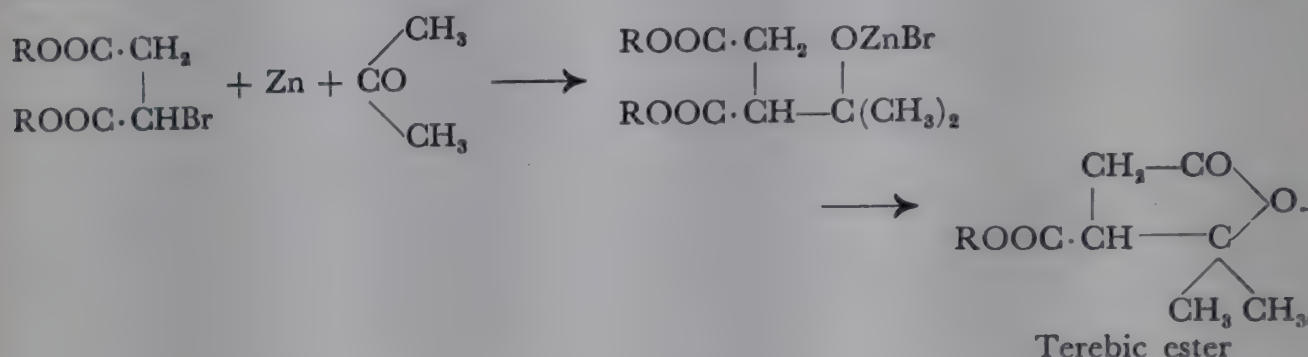
The commercial product "terpineol" is obtained from terpin hydrate (see p. 681) by dehydrating it with phosphoric acid, and consists of a mixture of α -, β -, and γ -terpineol, and terpinenol-1. All these alcohols possess a pleasant odour, reminiscent of lilac.

The constitution of α -terpineol has been arrived at from the products of its oxidation, and its total synthesis. Oxidation gives terebic acid (q.v.), *via* a series of intermediate products:

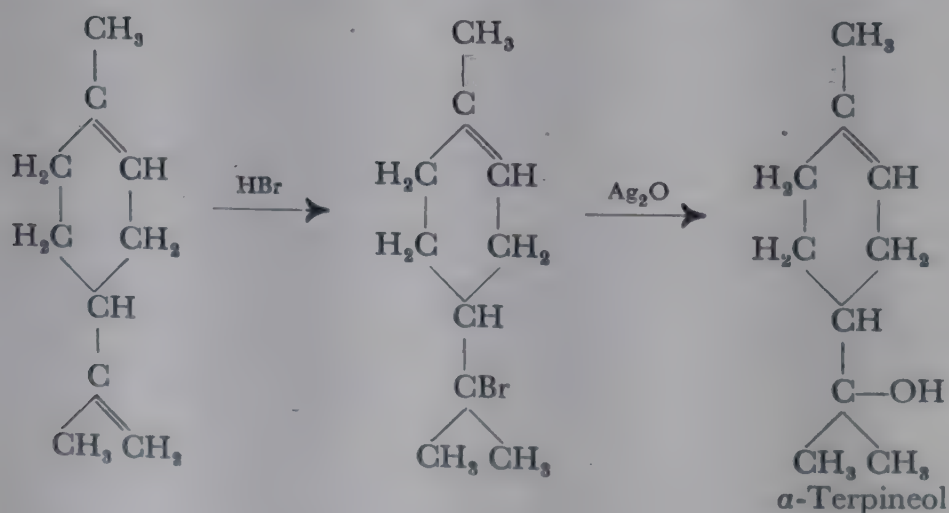




Terebic ester itself can be synthesized from bromosuccinic ester, zinc, and acetone:



One straightforward synthesis which proves the constitution of α -terpineol is that due to Perkin, already described (p. 672), which starts from γ -carboxylated pimelic acid. Limonene can also be used for the preparation of α -terpineol, a molecule of hydrogen bromide being added to give limonene hydrobromide, and the bromine in this being replaced by the hydroxyl group:



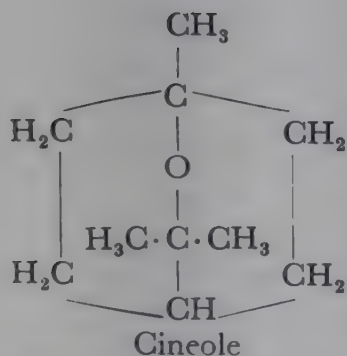
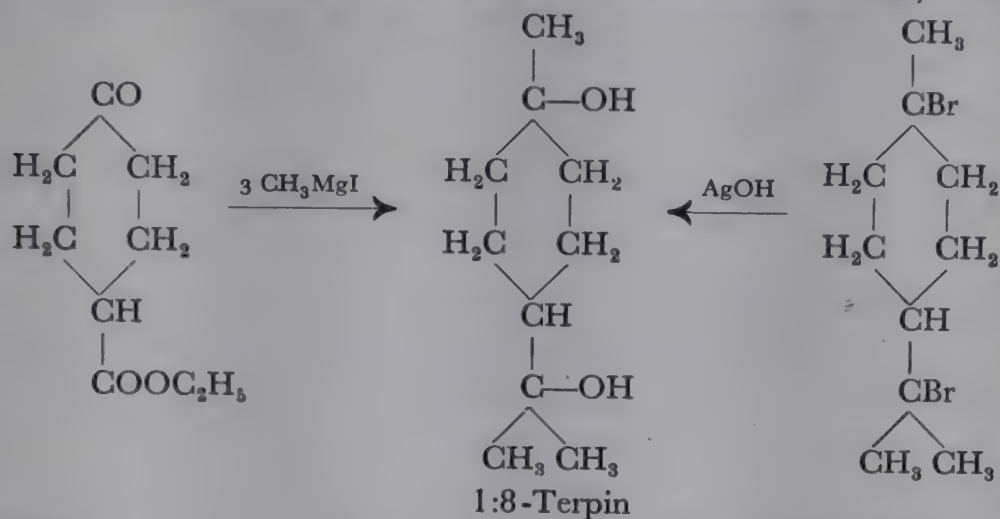
	M.p.	B.p.	$[\alpha]_D$
α -Terpineol	38-40°	217-218°	+98.5°
β -Terpineol	32-33°	209-210°	
γ -Terpineol	69-70°		
Terpinenol-1		208-210°	
Terpinenol-4		209-212°	+25.4°
Piperitol		100-106° (19 mm)	

The action of hydrogen bromide on α -, β -, and γ -terpineols gives 1:8-

dibromomenthane, and that on terpinenol-1 and terpinenol-4 gives 1:4-dibromomenthane.

TERPIN. The ordinary *terpin hydrate*, or the hydrate of 1:8-terpin, scarcely occurs in fresh essential oils, but is formed in some of them on long standing. It is produced technically from oil of turpentine by a process of hydration (with dilute sulphuric acid). It is used in the preparation of perfumes, particularly the terpeneols.

The constitution of 1:8-terpin follows from its synthesis, which is carried out by acting on *cyclohexanone-4-carboxylic ester* with methylmagnesium salt, or from 1:8-dibromomenthane by replacing the bromine with the hydroxyl group:

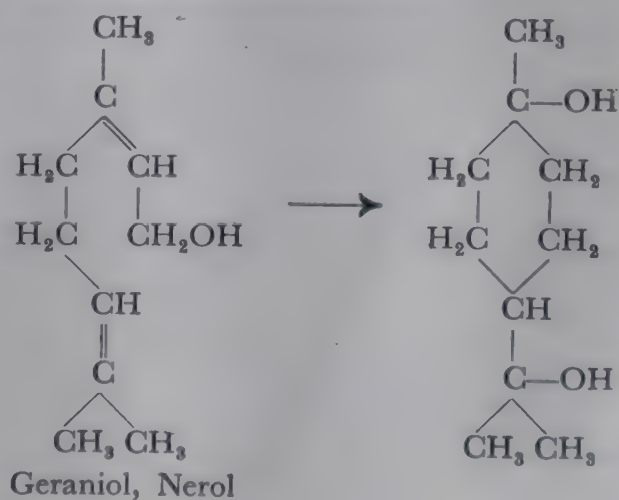


1:8-Terpin exists in two stereoisomeric forms. The *cis*-compound, which has the two hydroxyl groups in the *cis*-position, is readily formed from terpin hydrate if the latter is heated or allowed to stand over sulphuric acid. It melts at 104° , and can be converted into an anhydride, an intramolecular ether, *cineole* or *eucalyptol*, by removal of water (boiling with acids). Cineole smells camphor-like, melts at $+1^{\circ}$, and boils at $176-177^{\circ}$. It occurs in many essential oils, e.g. in the oil of *Eucalyptus globulus*, cajuput oil, and wormseed oil.

The ability of cineole to form addition compounds with acids (halogen hydracids, phosphoric acid, etc.), halogens, phenols, etc., is worthy of note. They belong to the class of oxonium salts.

The anhydrous *trans*-form of 1:8-terpin melts at 157° . It is formed, e.g. as its acetate, by the action of silver acetate on 1:8-dibromomenthane.

Geraniol and nerol (see p. 110) may be converted into 1:8-terpin hydrate by treatment with sulphuric acid. Nerol undergoes the ring-closure more rapidly than the stereoisomeric geraniol, and hence is considered as having the *cis*-configuration:



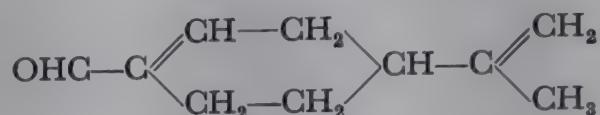
A second terpin is *1:4-terpin*, which is also known in a *cis*- and a *trans*-form. It is less important than the 1:8-isomeride. It can be synthesized from 1:4-dibromomenthane.

Dehydration of 1:4-terpin gives *1:4-cineole*. The same compound is contained in technical terpineol, and occurs in oil of cubeb. It boils at 173–174°.

Aldehydes and ketones of the cyclohexane series

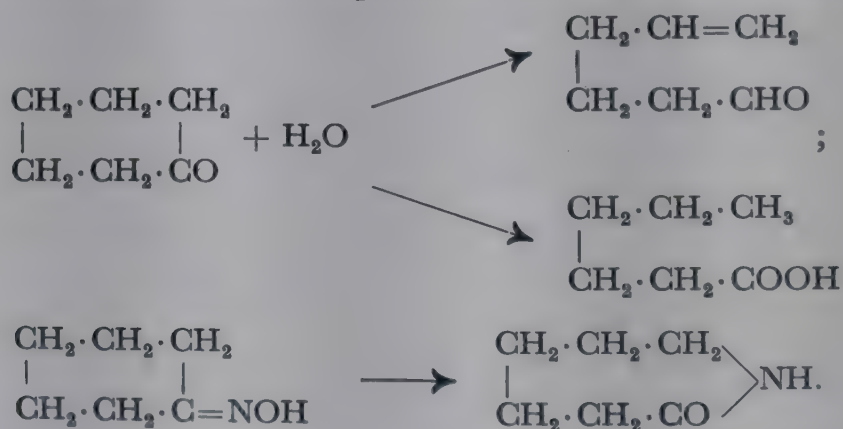
Aldehydes.

Perillaldehyde, discovered by Semmler in the essential oil of *Perilla nankinensis*, is an unsaturated aldehyde derived from *p*-menthane. Its anti-aldoxime is distinguished by an exceedingly sweet taste (see table XII):



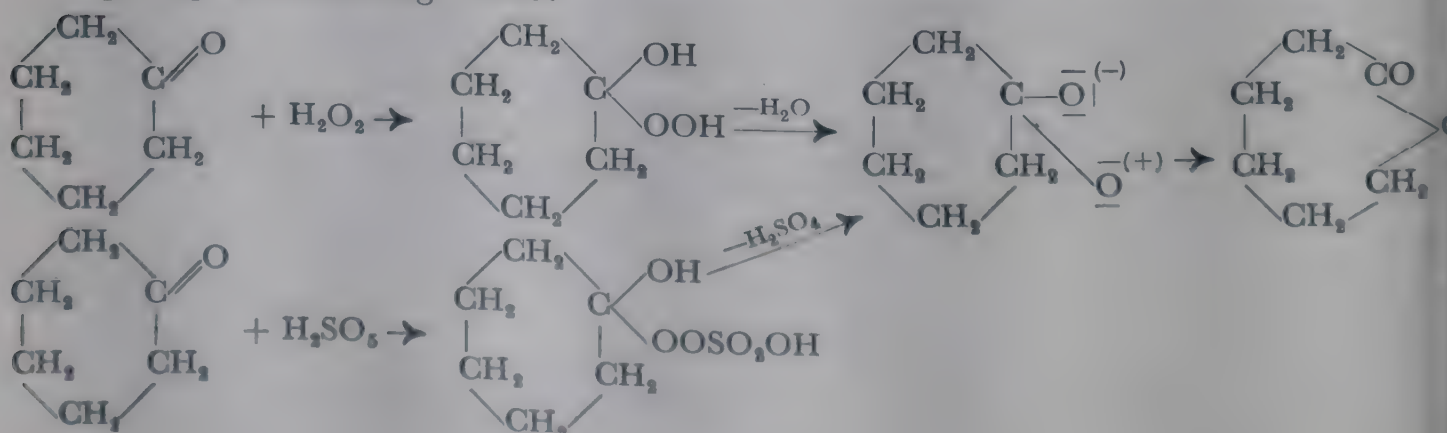
Saturated ketones.

CYCLOHEXANONE and its methods of preparation have already been mentioned several times. This very stable ketone boils at 156.5°. It has often been used as the starting point of syntheses. In alcoholic solution in sunlight its ring is ruptured with formation of caproic acid and Δ^5 -hexenaldehyde (Ciamician). Its oxime rearranges to the lactam of ϵ -aminocaproic acid under the action of sulphuric acid:

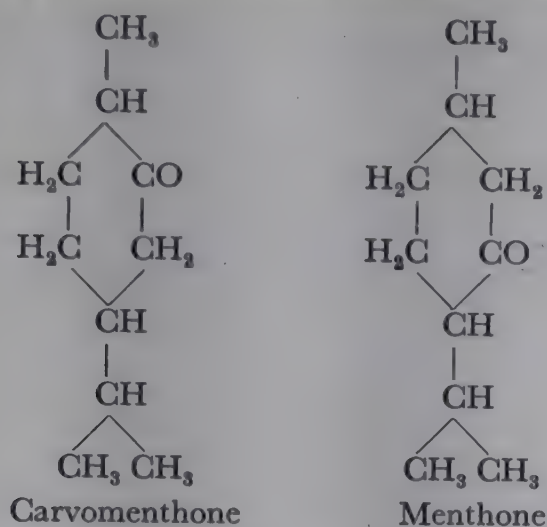


By the action of sulphur or selenium at 240°, *cyclohexanone* is dehydrogenated to phenol. Other hydroaromatic ketones behave similarly.

If Caro's acid or hydrogen peroxide is allowed to act upon cyclic ketones, they are oxidized to lactones. In the case of *cyclohexanone* the reaction takes perhaps the following course:

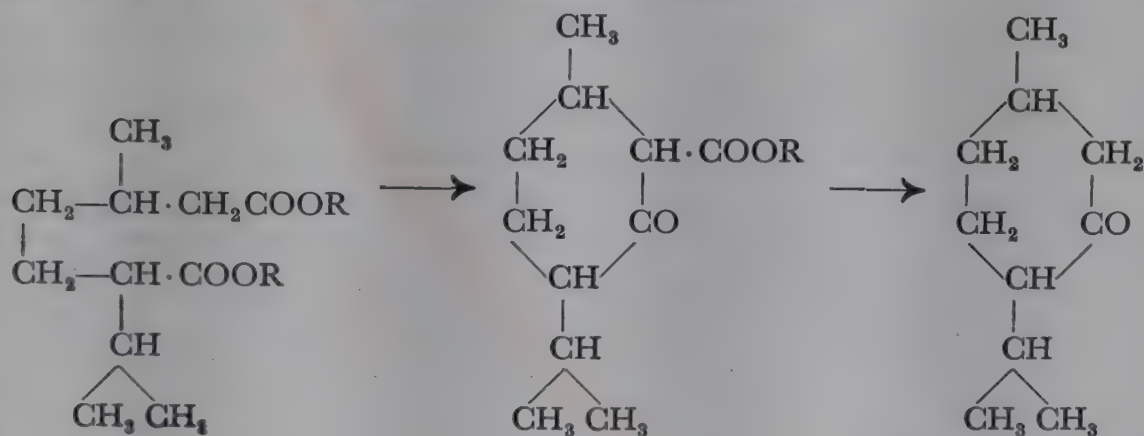


The saturated ketones *carvomenthone* and *menthone* are derived from *p*-menthane:



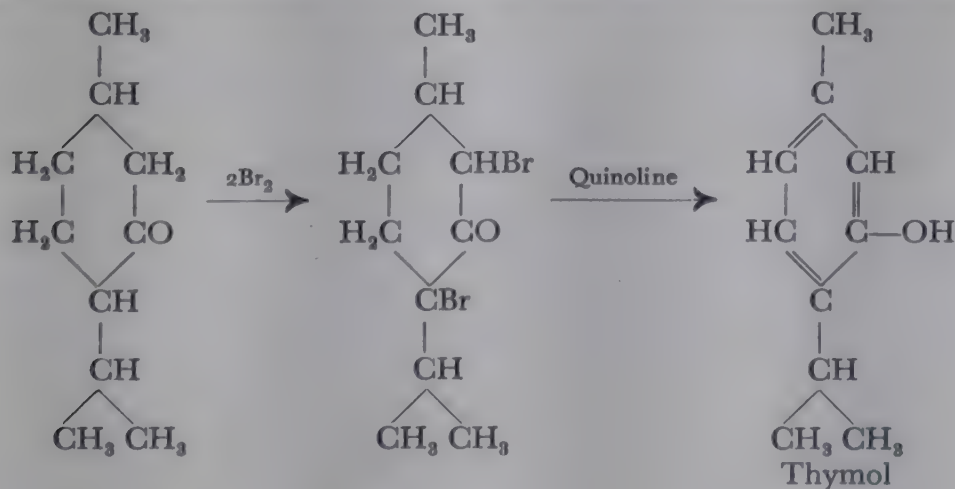
Menthone occurs in both the *d*- and *l*-form in essential oils, the first being contained, for example, in oil of pennyroyal, and the second in peppermint oil. *l*-Menthone is prepared synthetically from *l*-menthol by oxidation.

A total synthesis of menthone starts with β -methyl- α' -isopropylpimelic acid, whose ester is condensed by means of sodium ethylate:



l-Menthone has an odour of peppermint. It boils at 208° , $[\alpha]_D = -20^\circ$ to -26° . On treatment with sulphuric acid it isomerizes to *d*-isomenthone ($[\alpha]_D = +93^\circ$). (The two asymmetric carbon atoms of menthone mean the existence of two pairs of antipodes.) Isomenthone seems to occur in essential oils, e.g. the *l*-form in Réunion geranium oil. On hydrolysis of the oils, however, isomerization readily sets in, and *l*-menthone is formed.

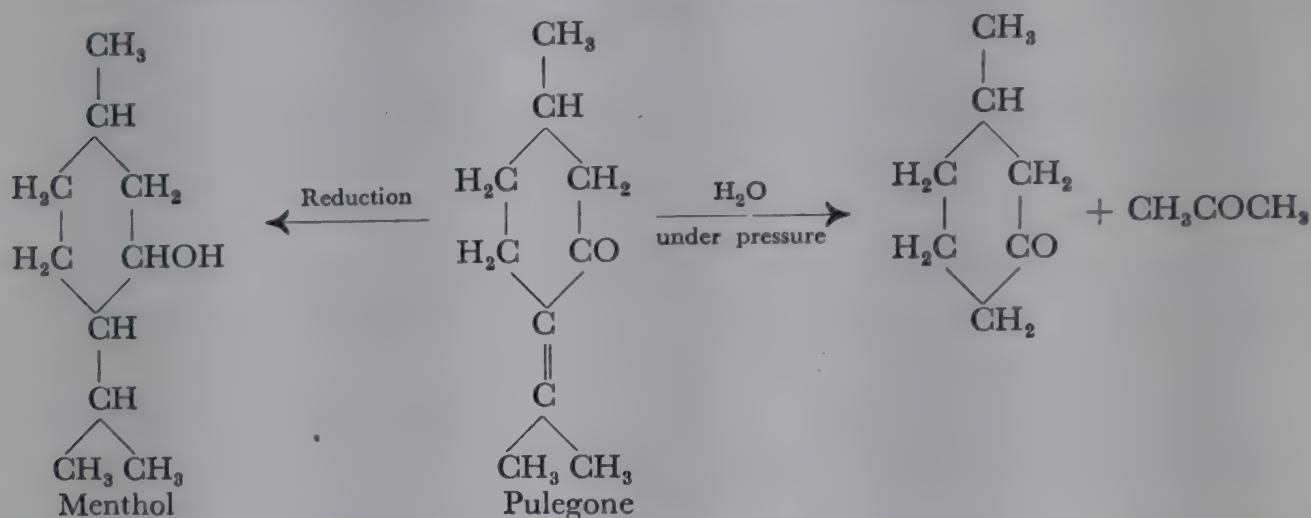
The degradation of menthone to thymol has been accomplished in the following way:



Unsaturated ketones.

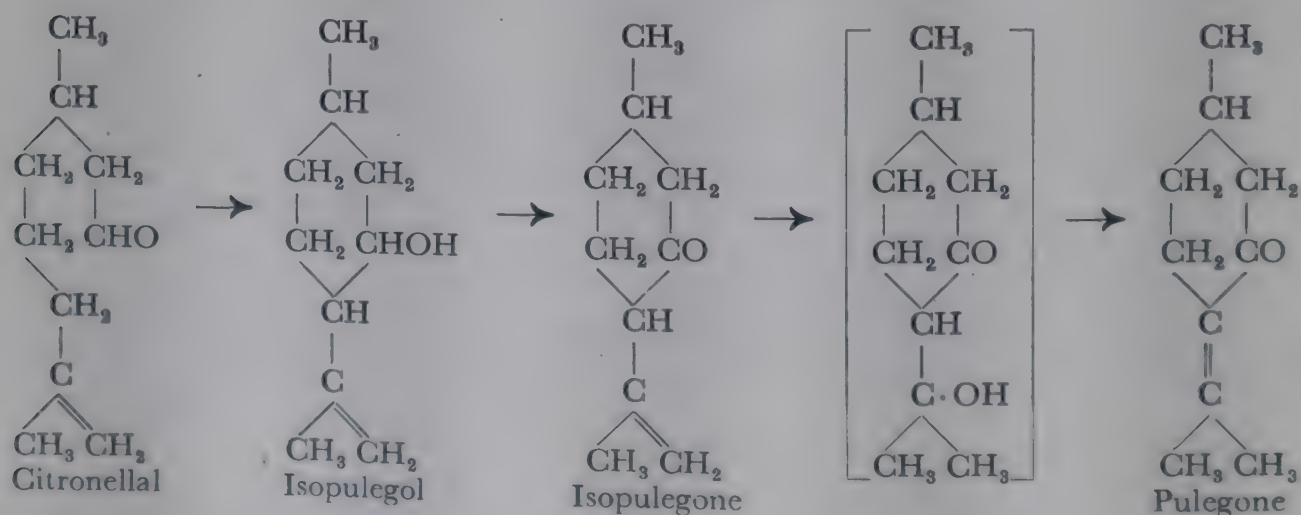
PULEGONE. This unsaturated ketone occurs in the dextrorotatory form as the chief constituent of oil of pennyroyal. It has a menthol-like odour and boils at 224° .

Pulegone can be reduced to menthol by means of nascent hydrogen. On heating with water under pressure it undergoes hydrolytic fission at the semicyclic double bond, *m*-methylcyclohexanone being formed:



The ring contraction of pulegone dibromide on treatment with alkali, forming pulegenic acid, has already been described on p. 643.

The synthesis of pulegone from citronellal is very interesting (Tiemann and Schmidt). If this natural aldehyde is boiled with acetic anhydride, it is converted into the acetate of isopulegol, which can be oxidized by chromic acid to isopulegone. Baryta rearranges isopulegone to pulegone, possibly through an intermediate hydrate which readily gives up water again:



By passing isopulegol under 25 mm pressure over glass-wool heated to 600° it is largely reconverted into citronellal (V. Grignard).

Δ^1 -*p*-Menthenone-3 occurs in Japanese peppermint oil, and some other natural essential oils. It is identical with the chief constituent of "piperitone", which is contained in large amounts in eucalyptus oils and peppermint oils. It boils at 235 – 237° .

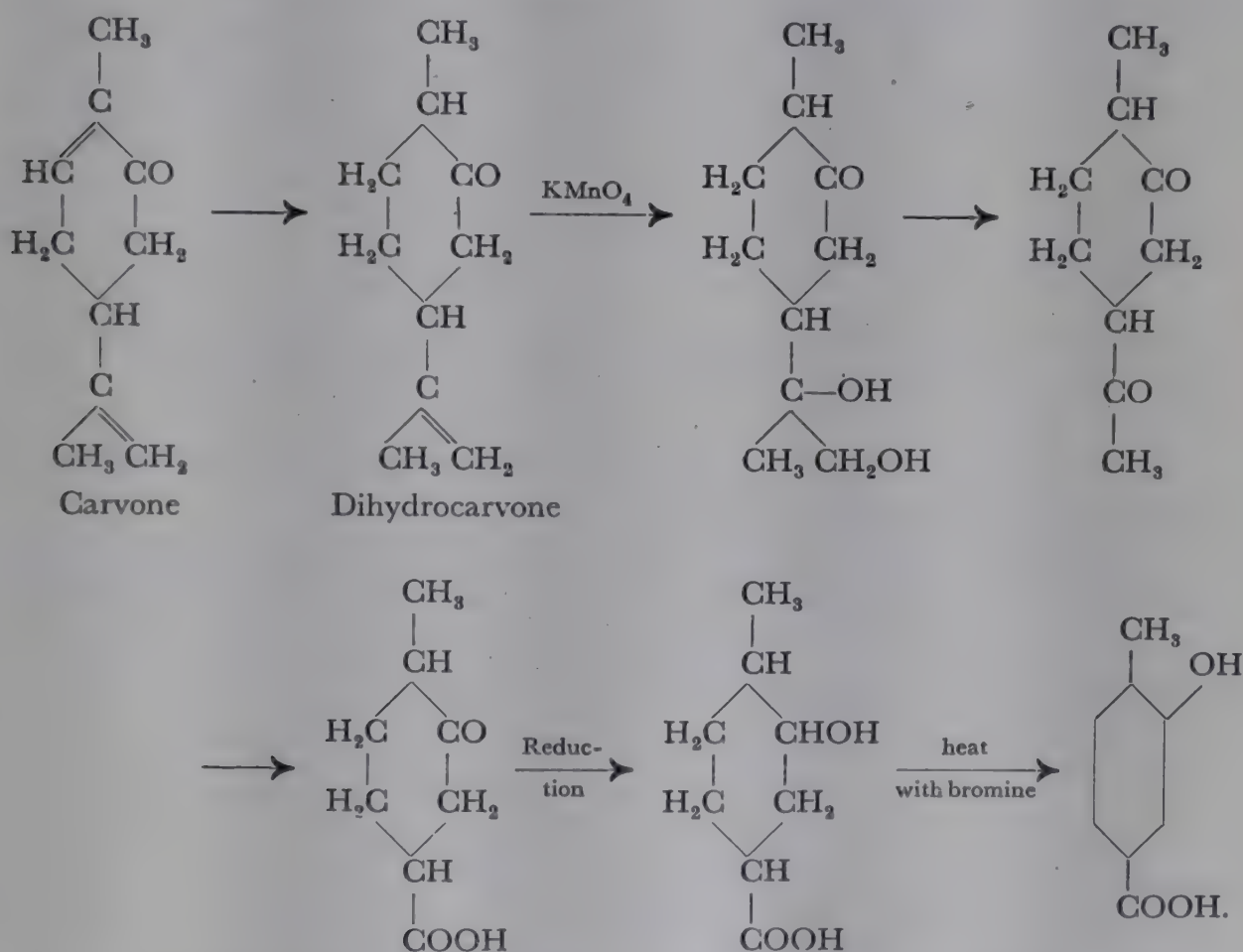
CARVONE. This important, doubly unsaturated ketone is very widely distributed

as the *d*-form, occurring, for example, in oil of caraway, and dill oil. The *l*-modification is found more rarely, for example, in kuromoji oil and spearmint oil. *dl*-Carvone has also been found in plants. Carvone has an odour of caraway, boils at 230–231°, and has a specific rotation $[\alpha]_D = +62^\circ$.

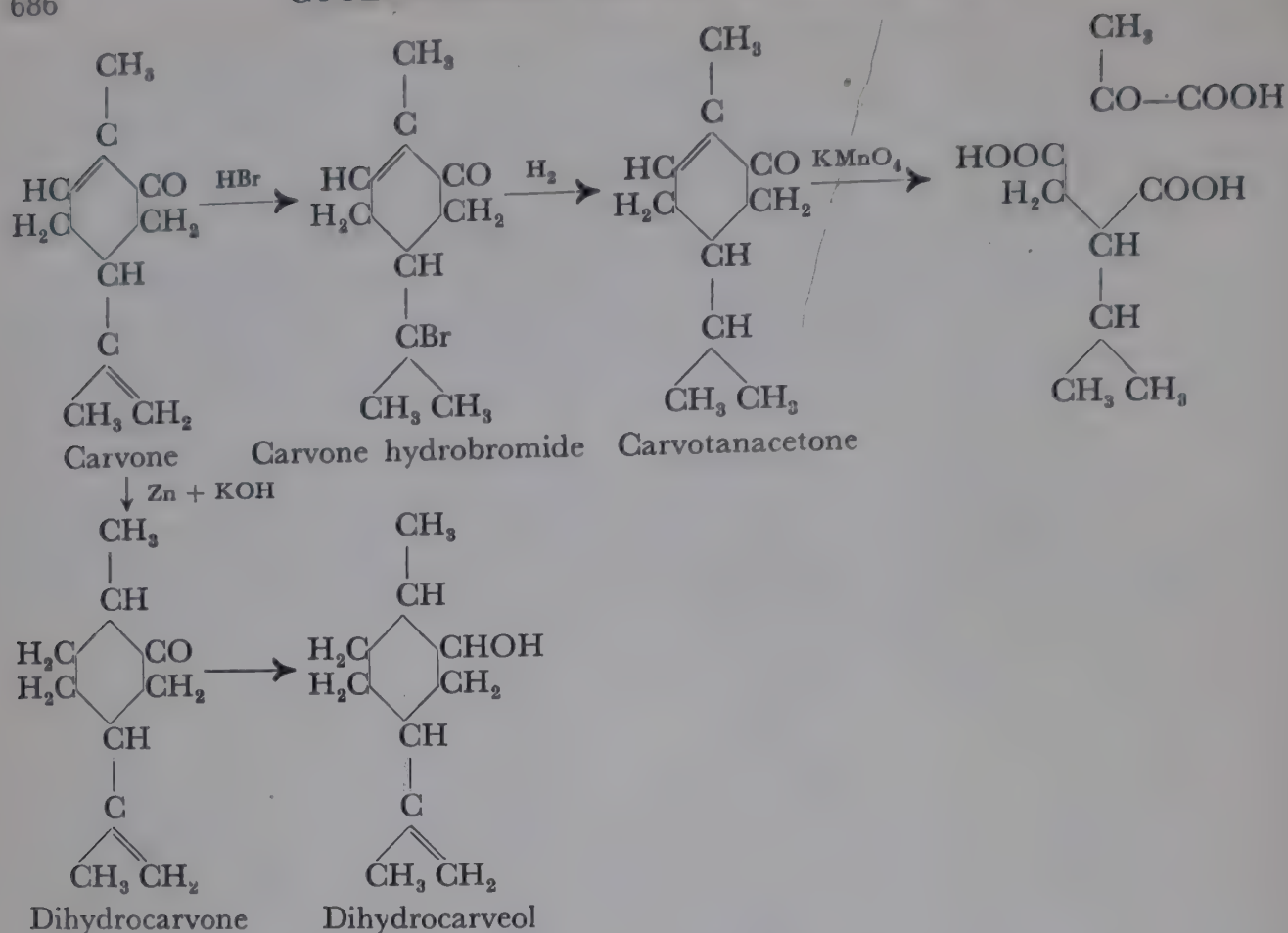
The constitution of carvone is established by the following facts:

1. The ketone can be very readily converted into a benzene derivative, carvacrol. The reaction occurs, e.g. when carvone is heated with sulphuric acid, phosphoric acid, or formic acid. The carbon skeleton and the position of the oxygen in carvone is thus determined (cf. formulation of the reaction, see p. 667).

2. The position of a double bond in position 8(9) follows from the fact that dihydrocarvone, which is formed from carvone by mild reduction, can be oxidized to 1-methyl-4-acetylcyclohexanone-2, of which the constitution is known from its degradation to *m*-hydroxy-*p*-toluic acid:



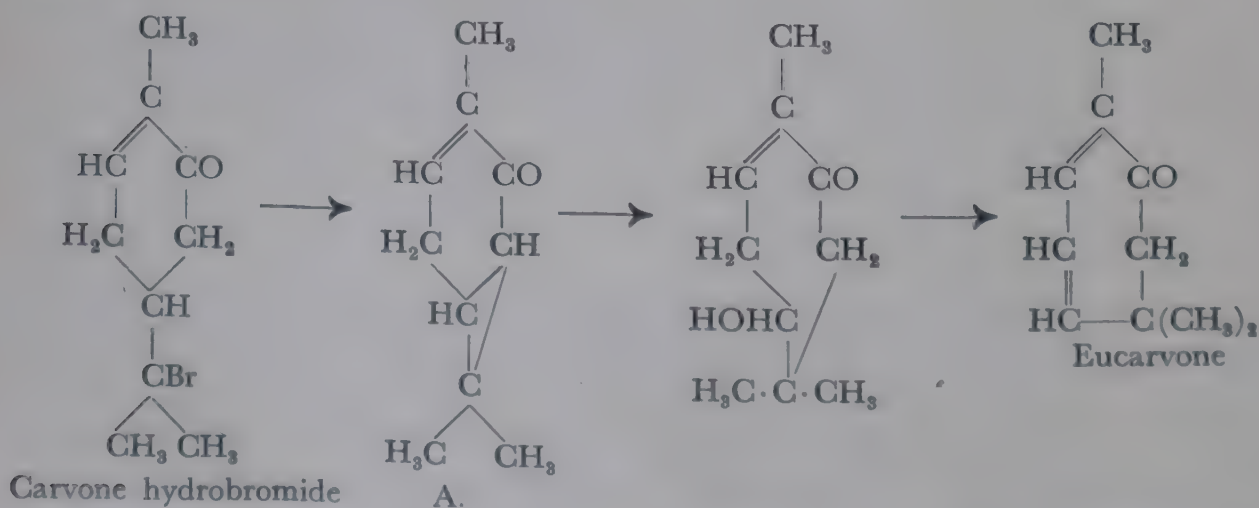
3. The position of the second double bond in carvone is suggested even by the behaviour of the ketone towards reducing agents. In the manner of other α,β -unsaturated ketones it is converted into *dihydrocarvone* by weak reducing agents (e.g. zinc and alcoholic alkali), and to *dihydrocarveol* by stronger reducing agents (sodium and alcohol). If one molecule of hydrogen bromide is added to carvone, and the bromine is removed by reduction from the carvone hydrobromide formed, *carvotanacetone*, isomeric with dihydrocarvone, is obtained. This must have the double bond between the carbon atoms 6 and 1, since on oxidation with permanganate it breaks down into pyruvic acid and *isopropylsuccinic acid*. Thus the position of the second double bond in carvone is established:



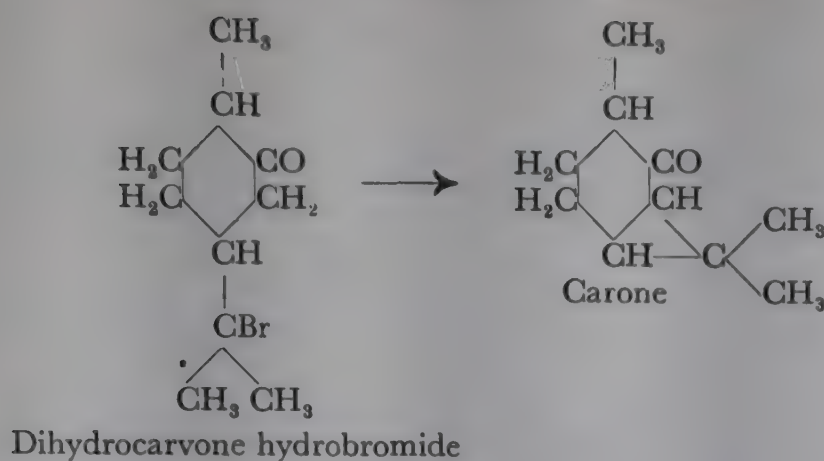
The preparation of carvone from dipentene (or limonene), and thus its total synthesis, has been mentioned on p. 671. If optically active *l*-limonene is chosen, *d*-carvone is obtained.

Two transformations of carvone into compounds of the *cycloheptane*, and mixed *cyclohexane-cyclopropane* types, are of interest.

If hydrogen bromide is eliminated from carvone hydrobromide, the *cycloheptane* derivative, *eucarvone* (Baeyer, Wallach) is formed with expansion of the ring. It boils at 85–87° (12 mm). A bicyclic unsaturated ketone of the carane series (A) is an intermediate product:

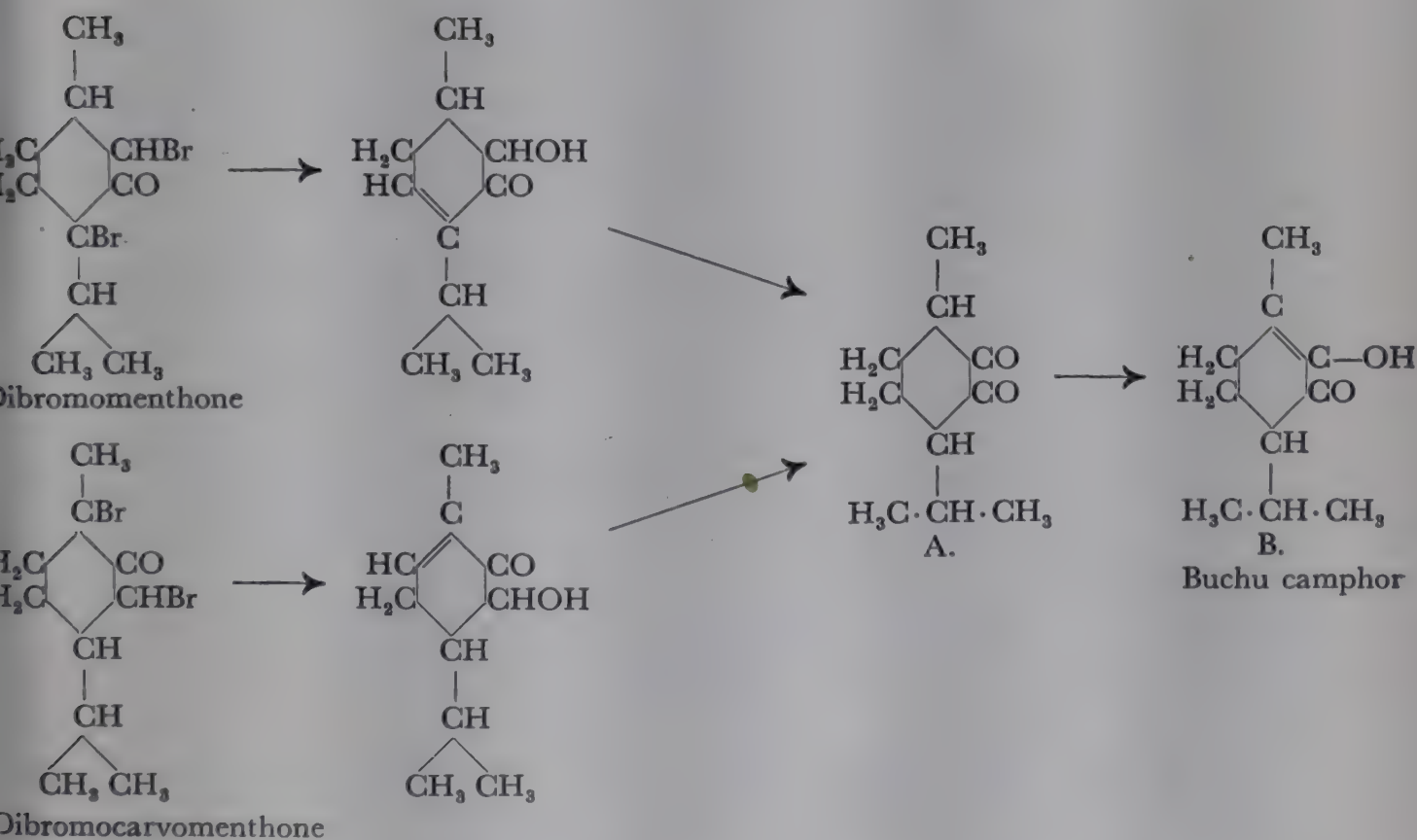


If, on the other hand, dihydrocarvone hydrobromide is prepared, and hydrogen bromide is removed from it by means of alcoholic potash, *carone*, a compound that has often been mentioned above and is very important in the chemistry of the bicyclic camphors, is formed:



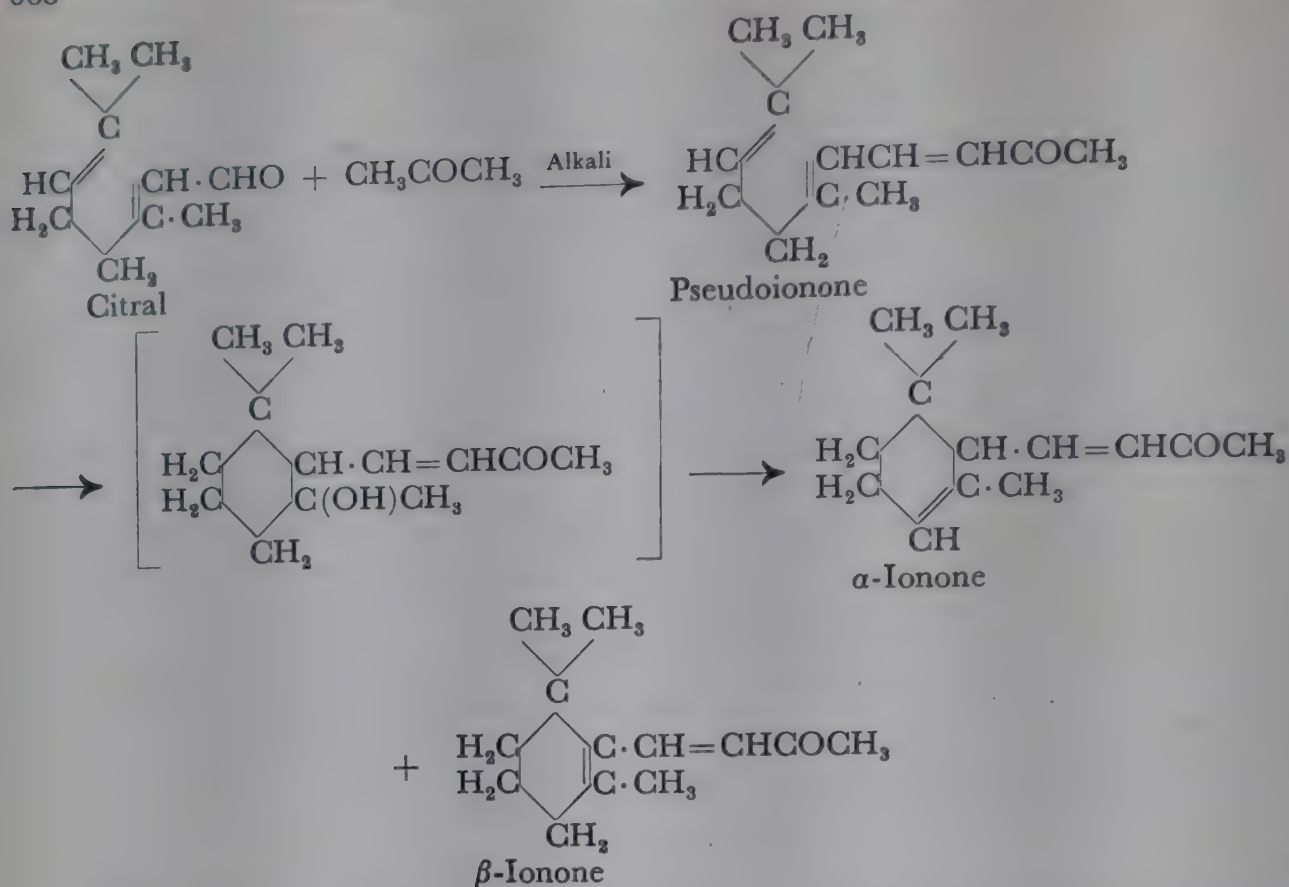
BUCHU CAMPHOR, or DIOSPHEENOL, is contained in the oil of buchu leaves (*Barosma*). It is optically inactive, melts at 83° , and boils at $109-110^{\circ}$ (10 mm).

The compound can be obtained synthetically from either dibromomenthone, or dibromocarvomenthone by shaking with dilute caustic potash. Although the formulation as the diketo form (A) must be considered in addition to the enol form (B), Buchu camphor appears to exist entirely in the form of the enol compound. It gives, for example, only a monoxime.



Exocyclic ketones of the cyclohexane series. The *ionones*, important, synthetically produced perfumes with an odour of violets, belong to this class.

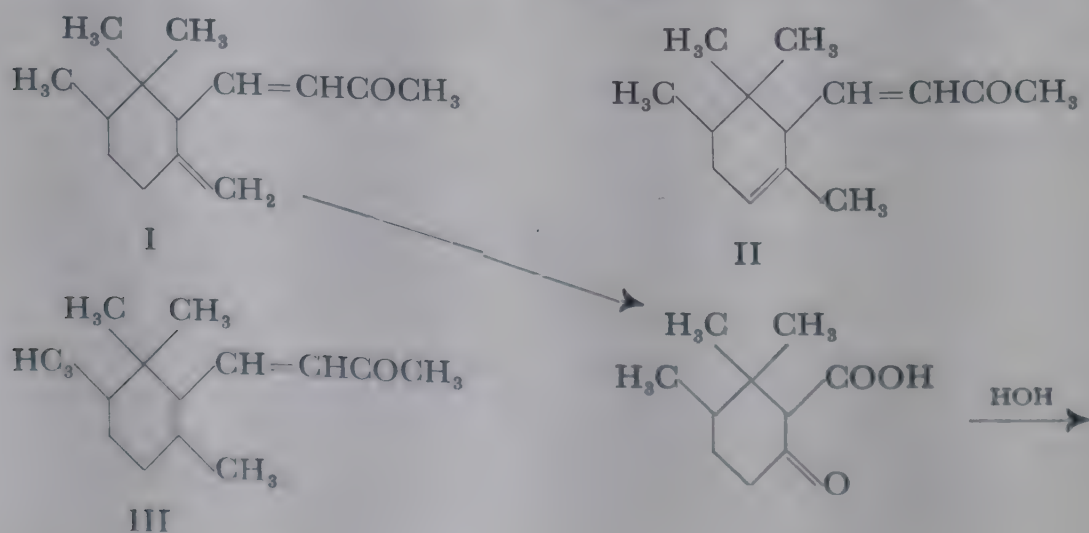
The synthesis of α - and β -ionone is due to Tiemann. If citral (see p. 171) is condensed with acetone in the presence of weak alkalis (baryta, soda, or sodium alcoholate), *pseudoionone* (b.p. $143-145^{\circ}$ (12 mm)) is formed. This is converted into a mixture of α - and β -ionone when heated with dilute sulphuric acid, or other acids. Hydrates are probably formed as intermediate products in the synthesis, which then lose water again:

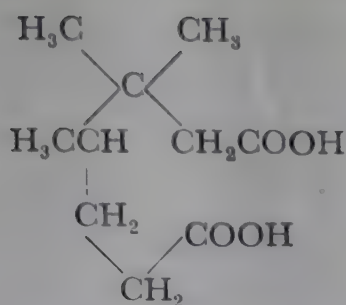


The separation of α -ionone and β -ionone is carried out with the aid of the bisulphite compounds, that of α -ionone being deposited from the aqueous solution in the form of beautiful leaflets on the addition of common salt.

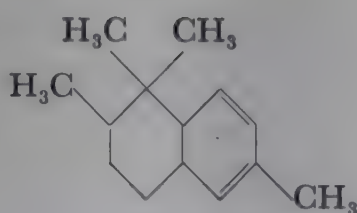
Concentrated ionone smells of cedar wood. The odour of violets only appears when the liquid is considerably diluted. α -Ionone boils at 127°, and β -ionone at 134° (both under 12 mm pressure). The β -bromophenylhydrazone of the α -compound melts at 142–143°, that of β -ionone at 116–118° (the semicarbazones melt at 107–108° and 148–149°, respectively). β -Ionone has been isolated from the balsam of *Boronia megastigma* Nees.

IRONE (b.p. 144° (16 mm)), the substance with a violet-like perfume contained in the root of *Iris florentina*, is, according to Ruzicka, a mixture of ketones, in which α -irone (II), γ -irone (I), and possibly also β -irone (III) are present (Y.-R. Naves, Ruzicka). Irone can be converted into irene (IV). On ozonolysis irone affords β,β,γ -trimethylpimelic acid (besides formic acid). This can be explained by a degradation of γ -irone, taking place in the following way:





Trimethylpimelic acid



IV

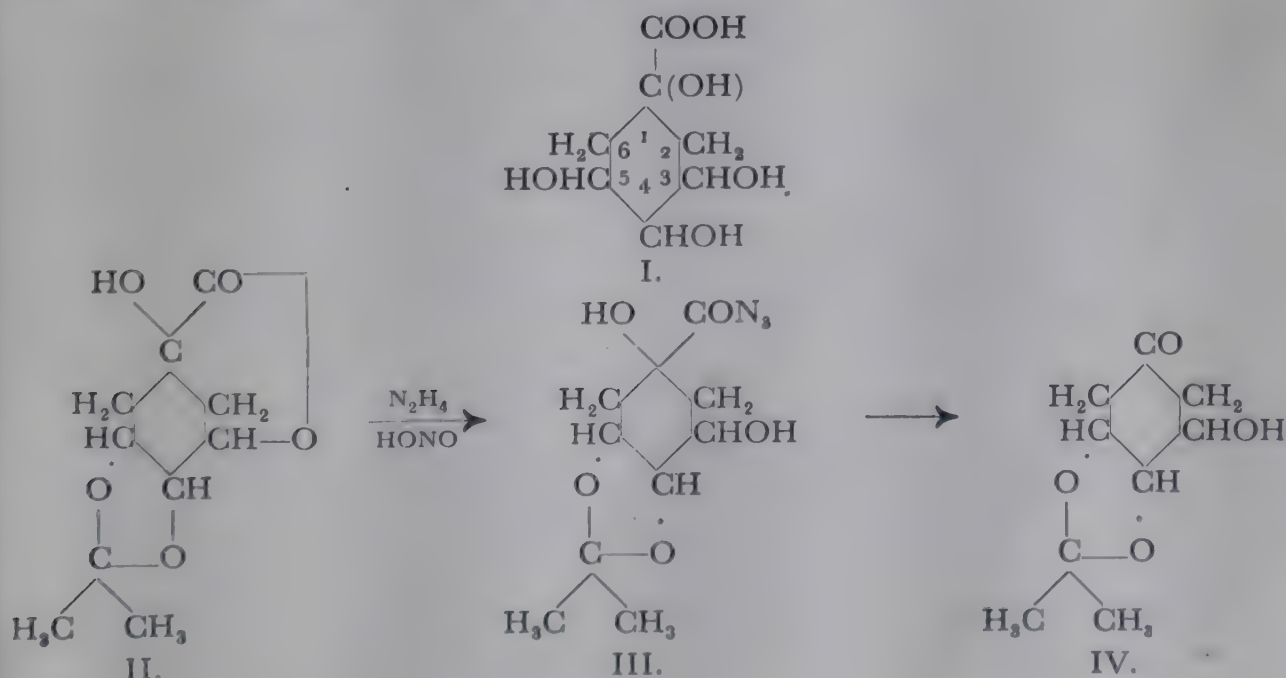
Carboxylic acids of the cyclohexane series

CYCLOHEXANEMONOCARBOXYLIC ACID has been prepared from benzoic acid by hydrogenation with sodium and alcohol, or with platinum and hydrogen in glacial acetic acid solution, and in other ways. It is, however, still relatively difficult to obtain, and is therefore of little importance. Its melting point is about 30° .

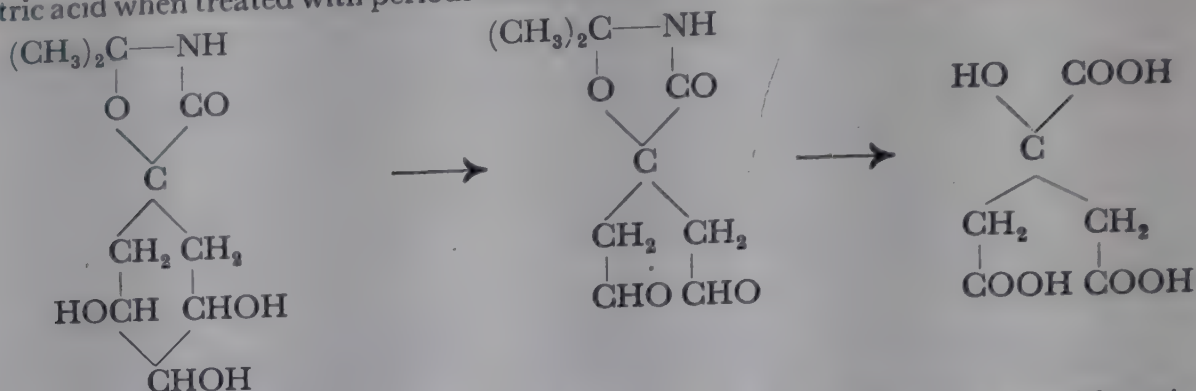
QUINIC ACID. This important acid is of wide occurrence in plants. It is found in large quantities in cinchona bark, coffee beans (it forms in this case a component of the so-called *chlorogenic acid*), in hay, and in the leaves of many plants, e.g. beets.

Its composition, and the fact that it is readily converted into benzene derivatives, show it to be a tetrahydroxycyclohexanecarboxylic acid. Of the four hydroxyl groups, one is attached to the same carbon atom as the carboxyl group, since, like other α -hydroxycarboxylic acids, quinic acid loses one molecule of carbon monoxide when treated with sulphuric acid. Two hydroxyl groups must be in the *para*- and *meta*-positions with respect to the COOH-group, because quinic acid can be very easily converted into protocatechuic acid. The fourth hydroxyl group takes up the second *meta*-position to the carboxyl. This follows from the following degradation reactions (H. O. Fischer):

Quinic acid (I) forms the acetone-quinide (II) when treated with acetone and hydrogen chloride. This has been converted into the azide (III) by the action of hydrazine and nitrous acid, which gave the acetone compound of trihydroxycyclohexanone (IV) on undergoing the Curtius degradation. The compound (IV) yields a phenylhydrazone, but no phenylosazone, and therefore does not contain a hydroxyl group adjacent to the keto-group:

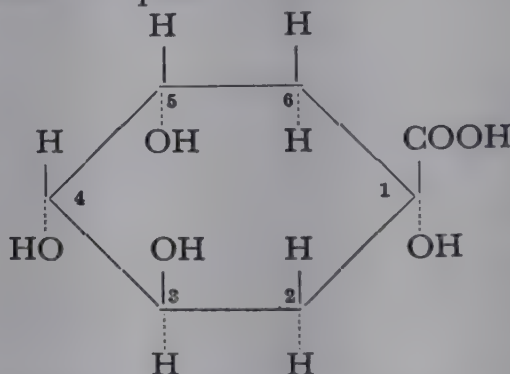


The acetone compound of the amide of quinic acid is degraded to the dialdehyde of citric acid when treated with periodic acid. This compound is readily oxidized to citric acid:



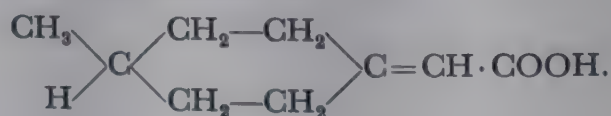
The configuration of quinic acid is arrived at by the following considerations:

The hydroxyl-groups 4 and 5 are in the *cis*-position, since they combine with acetone to give a five-membered ring, this being a property only of the *cis*-forms of *cyclohexane*-1:2-diols. The carboxyl group and the hydroxyl group in position 3 are also in the *cis*-position, as *trans*-lactones are unstable. Finally, the pair of hydroxyl groups in positions 4 and 5 are in the *trans*-position to the carboxyl, since the 3-methyl ether of quinic acid does not form a lactone. This leads to the following stereo-formula for quinic acid:

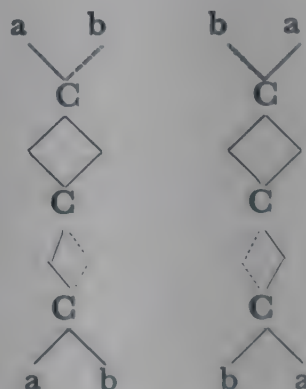


In *chlorogenic acid*, the hydroxyl of quinic acid in position 3 is esterified with caffeic acid; see also p. 543.

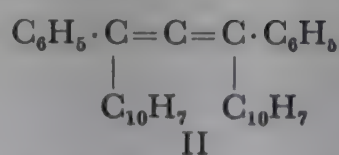
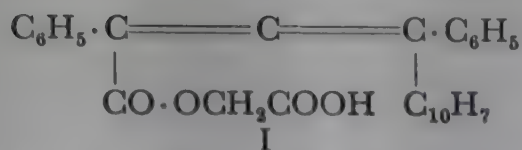
***p*-METHYLCYCLOHEXYLIDENEACETIC ACID.**



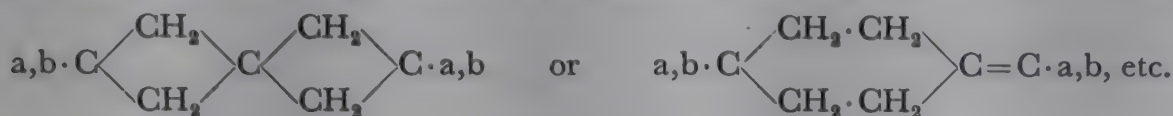
van 't Hoff has pointed out that allene derivatives of the general type $\text{a}, \text{b} \cdot \overset{1}{\text{C}}=\overset{2}{\text{C}}=\overset{3}{\text{C}} \cdot \text{a}, \text{b}$ have an unsymmetrical structure, and hence must occur in mirror-image isomerides:



Simple compounds of this type are rather difficult to prepare, so that it has been possible only recently to test the question experimentally. These experiments have led to a confirmation of van 't Hoff's prediction. Thus, E. P. Kohler and his co-workers have been able to prepare the ester of α, γ -diphenyl- γ -naphthylallene-carboxylic acid with glycolic acid (I), and W. H. Mills and Maitland diphenyl-di- α -naphthylallene (II), in optically active forms:

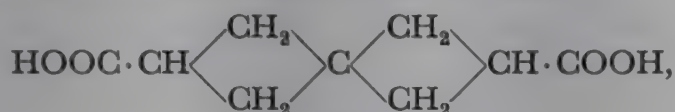


It is not difficult to see that, in principle, the same type of isomerism must also occur if, between the carbon atoms 1, 2, and 3 of the above allene derivative, two or four identical ring-members are inserted, instead of double bonds, e.g.:



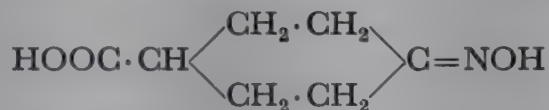
4-Methylcyclohexylideneacetic acid is a compound of this kind, and it has actually been prepared in optically active forms (Perkin and Pope). The substance melts at 52.5–53°, and has a specific rotation $[\alpha]_{\text{D}} = \pm 81.4^\circ$ in alcohol.

SPIROHEPTANEDICARBOXYLIC ACID¹ (H. J. Backer),



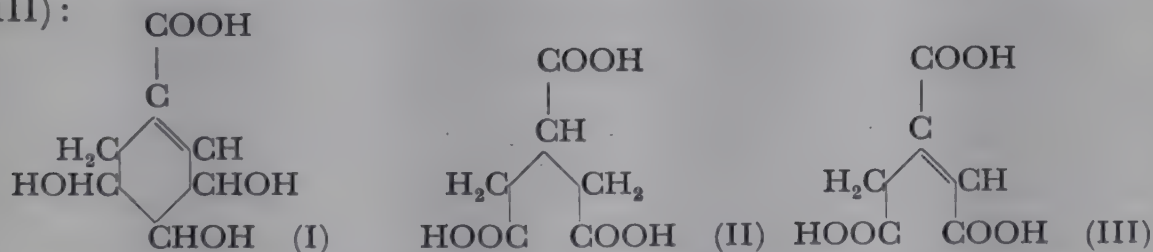
furthermore, belongs to the same class. The specific rotation of its ammonium salt is $[\alpha]_{\text{D}} = +0.13^\circ$.

Also, the oxime of a cyclohexanonecarboxylic acid,

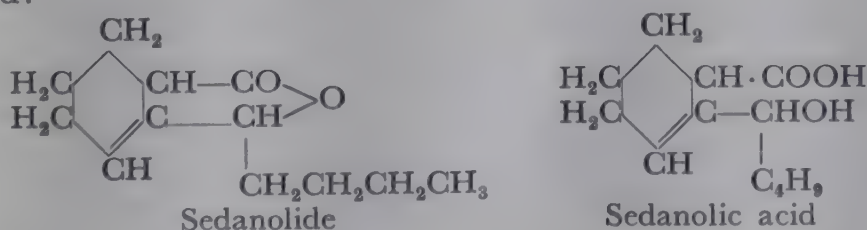


has been resolved into optically active isomerides.

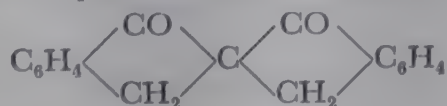
SHIKIMIC ACID, a constituent of the fruit of *Illicium religiosum*, is related to quinic acid. It has the constitution I. Dihydroshikimic methyl ester is degraded by periodic acid to tricarballic acid (II), whilst shikimic acid itself gives *trans*-aconitic acid (III):



SEDANOLIDE, (b.p. 185° (17 mm)), the odoriferous principle of oil of celery, is also derived from a cyclohexenemonocarboxylic acid. Ciamician and Silber have demonstrated that it has the following formula. Sedanolide is the lactone of sedanolic acid:

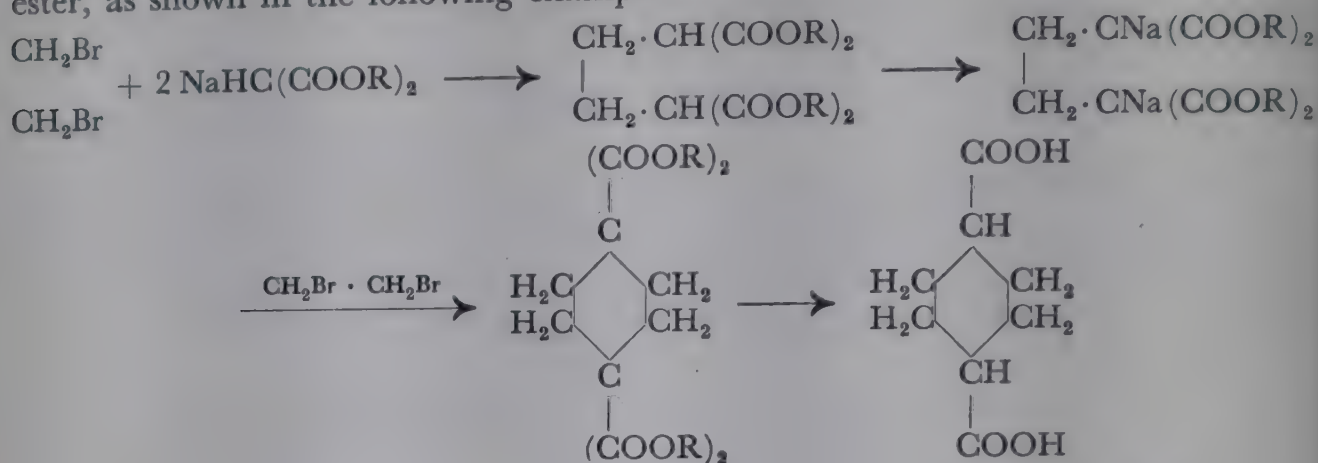


¹ By "spiranes" is understood compounds in which a C-atom is linked to 4 other C-atoms, in such a way that each pair belongs to a ring, as for instance,



Many spiranes have an asymmetric structure.

The three position-isomeric *cyclohexanedicarboxylic acids*, *hexahydrophthalic acid*, *hexahydroisophthalic acid*, and *hexahydroterephthalic acid*, are all known in *cis*- and *trans*-forms. They are prepared by reduction of the corresponding phthalic acids. Sodium and alcohol, or platinum oxide and hydrogen, serve as reducing agents. It is also possible to synthesize *cyclohexanedicarboxylic acids* by means of malonic ester, as shown in the following example:



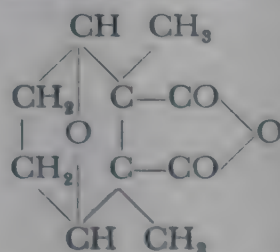
	M.p. of the <i>cis</i> -form	M.p. of the <i>trans</i> -form
Hexahydrophthalic acid	192°	215°
Hexahydroisophthalic acid	163°	148°
Hexahydroterephthalic acid	161°	200°

Both *cis-trans*-isomeric hexahydrophthalic acids give anhydrides. That of the *trans*-compound is, however, labile, and readily isomerizes (on melting) into the stereoisomeric form. (The two carboxyl groups probably do not stand in a true *trans-trans*-position in this case, in consequence of the mobility of the *cyclohexane* ring — seat and tub forms, p. 663 — but in a “*meso-trans*”-position spatially more favourable for ring-closure).

In the case of the hexahydroisophthalic acids only one anhydride, that of the *cis*-form, is known. The two hexahydroterephthalic acids are converted into polymeric anhydrides on heating with acetyl chloride. On heating in a vacuum, these depolymerize and are converted into the monomolecular anhydride of *cis*-hexahydroterephthalic acid, which melts at about 160°, and can be split up to give *cis*-hexahydroterephthalic acid. By heating with hydrochloric acid to 180° the *cis-cyclohexanedicarboxylic acids* isomerize into the *trans*-forms.

In agreement with the requirements of theory the *trans*-forms of hexahydrophthalic acid and hexahydroisophthalic acid have been resolved into optically active isomerides. The melting point of the active hexahydrophthalic acids is 179–183°, $[\alpha]_D = \pm 18.5^\circ$ (A. Werner); the melting point of the active hexahydroisophthalic acids is 134°, $[\alpha]_D = \pm 23.4^\circ$ (Böeseken). The two hexahydroterephthalic acids are, on the other hand, symmetrical, and non-resolvable.

CANTHARIDIN, $\text{C}_{16}\text{H}_{12}\text{O}_4$, a poison contained in Spanish flies and other beetles, must be regarded as a somewhat more complicated derivative of a *cyclohexanedicarboxylic acid*. According to Gadamer it has the following formula, which has been confirmed by a synthesis due to K. Ziegler:



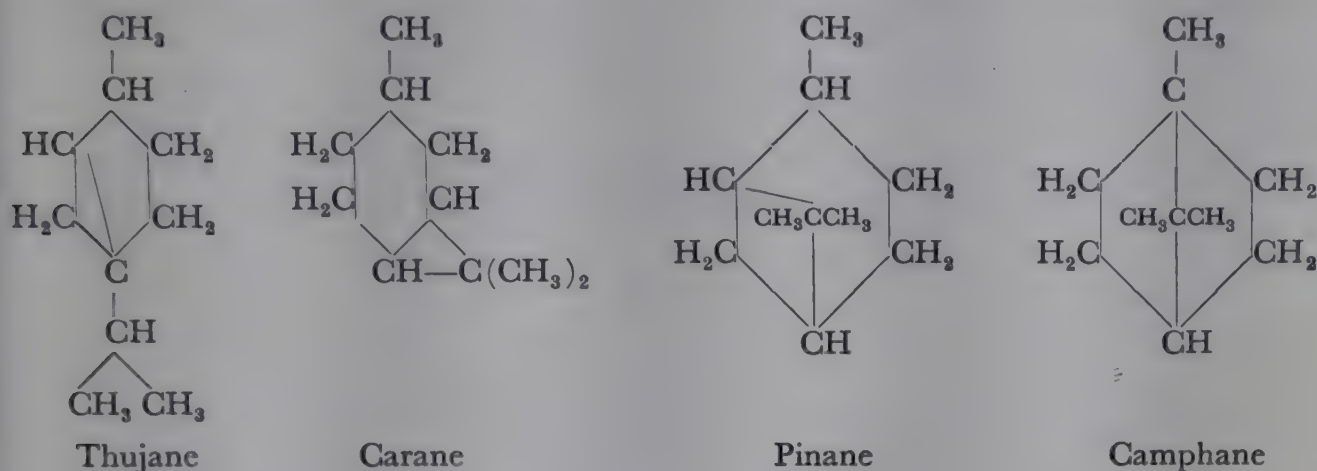
It melts at 218°. The compound raises blisters on the skin and gives rise to local inflammation.

CHAPTER 55

BICYCLIC TERPENES AND CAMPHORS

(WITH A SIX-MEMBERED RING)

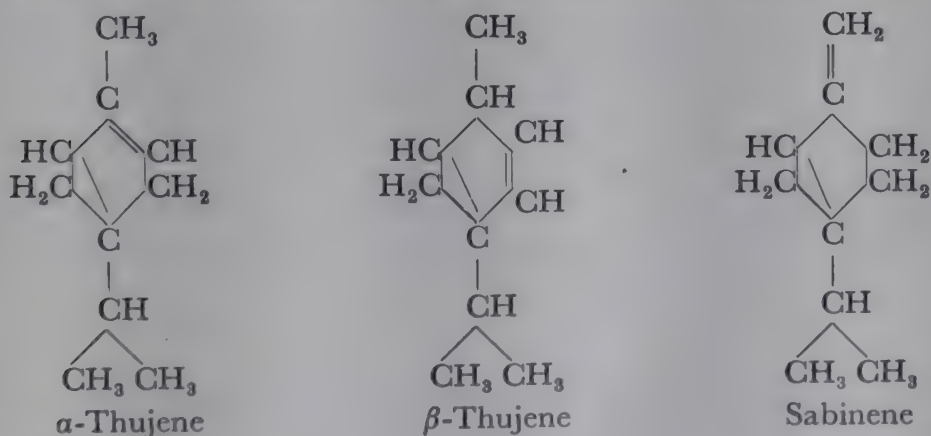
The naturally occurring bicyclic terpenes and camphors, which are very abundant and important, are almost all derived from *p*-menthane, and are to be considered chiefly as derivatives of the following parent substances:



Thujane group

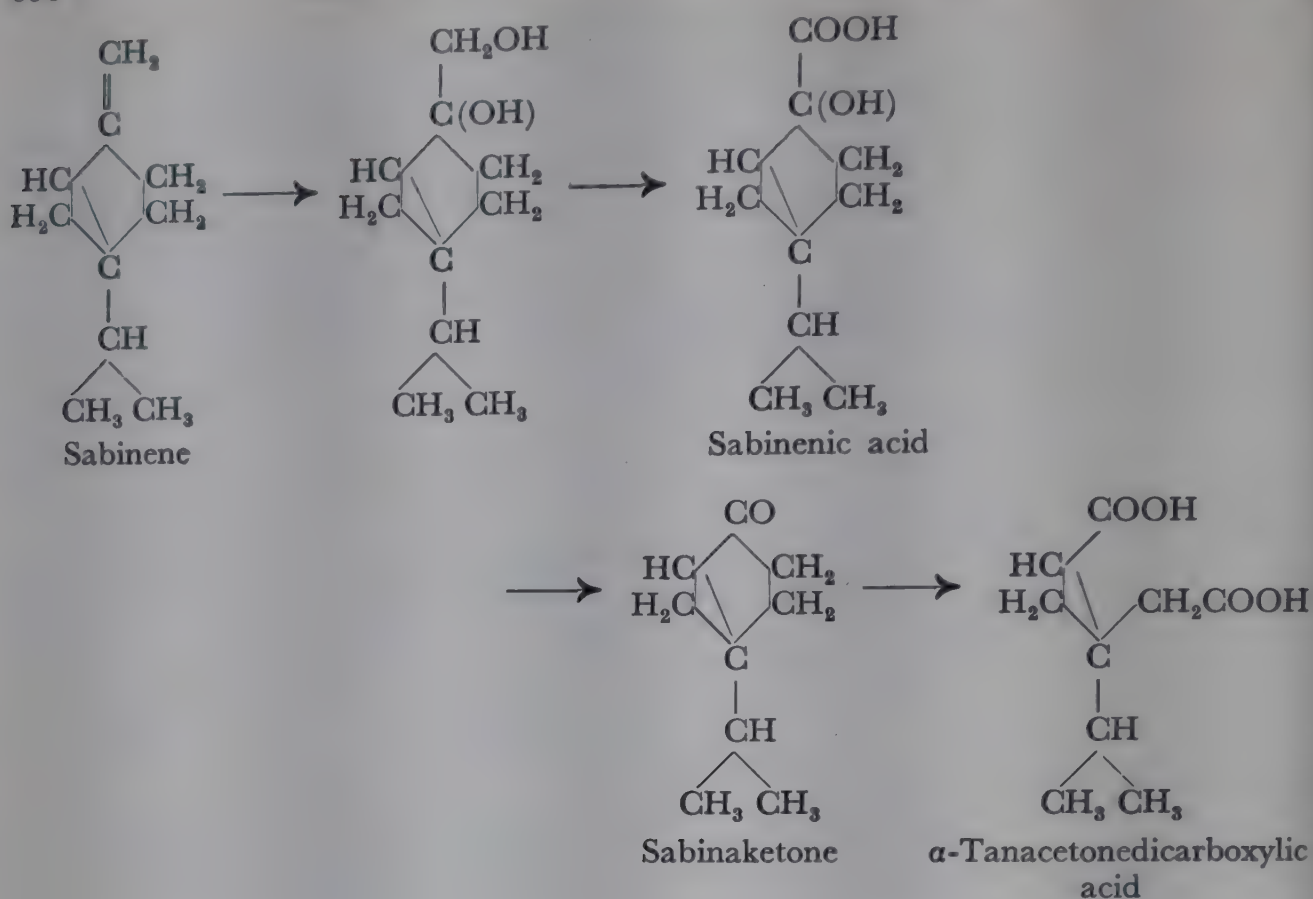
Thujane itself has been obtained by the catalytic reduction of sabinene and thujene with hydrogen and platinum (Tschugaeff). It can also be obtained from thujone (p. 694), and by total synthesis (Guha). It boils at 157°. It has not been definitely detected in nature.

α - and β -*thujene* and *sabinene* are singly unsaturated derivatives of thujane:

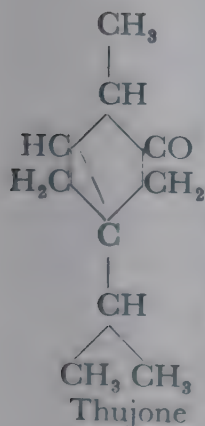
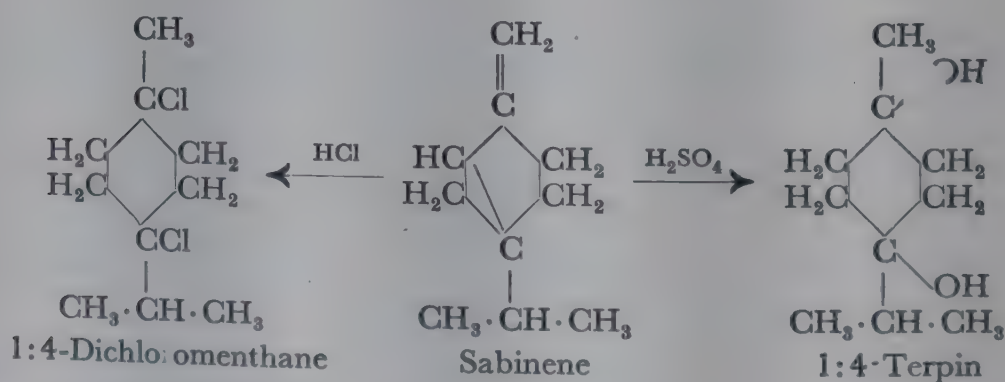


α - and β -*thujene* have only been obtained synthetically. On the other hand, *sabinene* belongs to the widely spread terpenes of essential oils. It is found particularly abundantly in oil of savin, Ceylon cardamom oil, oil of marjoram, etc. It boils at 162–166°.

Sabinene is oxidized by potassium permanganate to sabinaketone, and finally to α -tanacetonedicarboxylic acid. The nature of these oxidation products makes it possible to infer the position of the double bond and the existence of the *cyclopropane* ring in sabinene:



The cyclopropane ring of sabinene and other thujane derivatives can be readily opened by the most diverse reagents. Thus, hydrogen chloride produces with sabinene dissolved in glacial acetic acid 1:4-dichloromenthane, and dilute sulphuric acid converts it into 1:4-terpin:

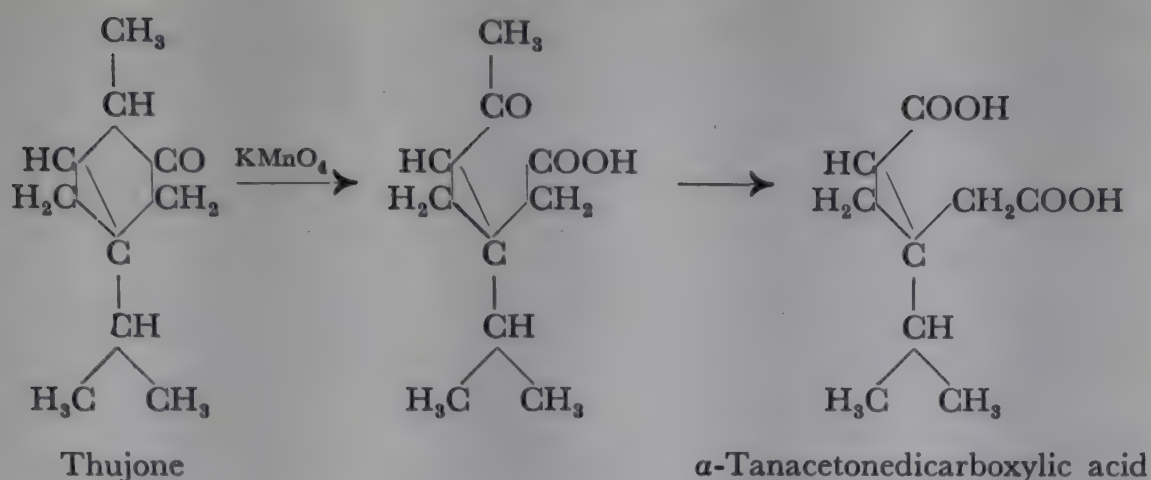


THUJONES. α - and β -thujone (tanacetone) are two isomeric ketones of the thujane series. Both correspond to the accompanying formula. They are stereoisomerides, but not antipodes, differing only by the configuration of carbon atom 1.

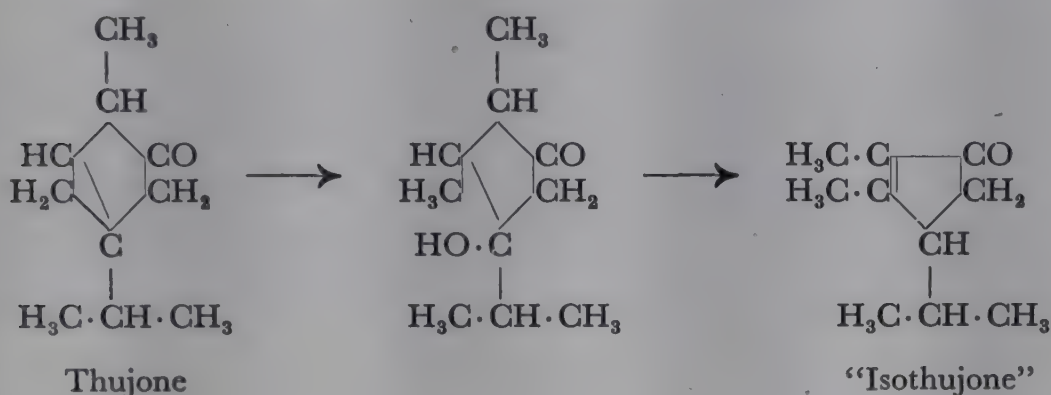
α -Thujone is found, for example, in thuja oil and oil of wormwood. It boils at 200–201° and has a specific rotation $[\alpha]_D = -19.9^\circ$.

β -Thujone has been isolated from tansy oil, for example, etc. It is dextrorotatory, $[\alpha]_D = +72.4^\circ$. Recently the following designations have been suggested: *d*-isothujone for β -thujone and *l*-thujone for α -thujone.

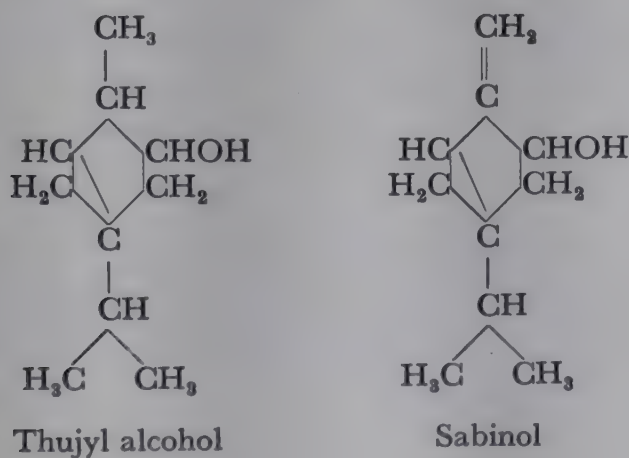
On heating to 280° thujone isomerizes to carvotanacetone (see p. 685), and on oxidation with permanganate it gives α -tanacetonedicarboxylic acid:



Warming with 40 % sulphuric acid destroys the trimethylene ring of thujone and gives "isothujone", a ketone derived from *cyclopentene* (Wallach, Semmler):



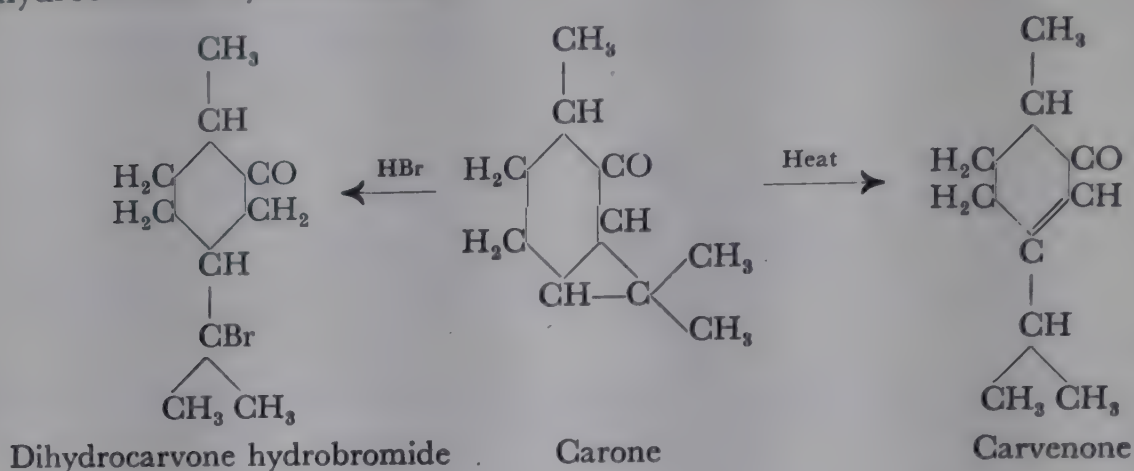
Reduction of thujone gives *thujyl alcohol* (and the stereoisomeric *l*-neothujyl alcohol and isothujyl alcohol). The compound is also found in essential oils, e.g. oil of wormwood. It contains two hydrogen atoms more than *sabinol*, of which the occurrence in oil of savin has been noted:



Carane group

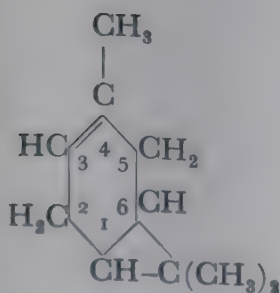
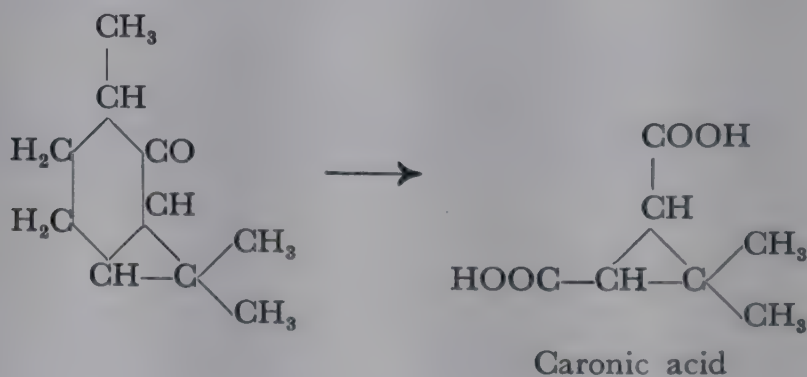
The first and most important member of this group, discovered by Baeyer, is *carone*. Its synthesis from dihydrocarvone hydrobromide is given on p. 687. Carone boils at about 210°, is optically active, and possesses an odour resembling camphor and peppermint.

Its trimethylene ring is easily opened. Thus, prolonged heating of carone brings about isomerization to carvenone, and with hydrogen bromide it gives dihydrocarvone hydrobromide:



Whilst in these examples the rupture of the trimethylene ring takes place so that the *isopropyl* radical keeps its position at carbon atom 4, the series of reactions given on p. 673, on the other hand, leads to a *m*-menthane derivative, carvestrene.

In contrast, it is possible to oxidize carone whilst maintaining the *cyclo*-propane ring, obtaining a simple trimethylene derivative, *caronic acid*. Together with the isomerization of carone referred to above, the result of this oxidation establishes the constitution of carone:

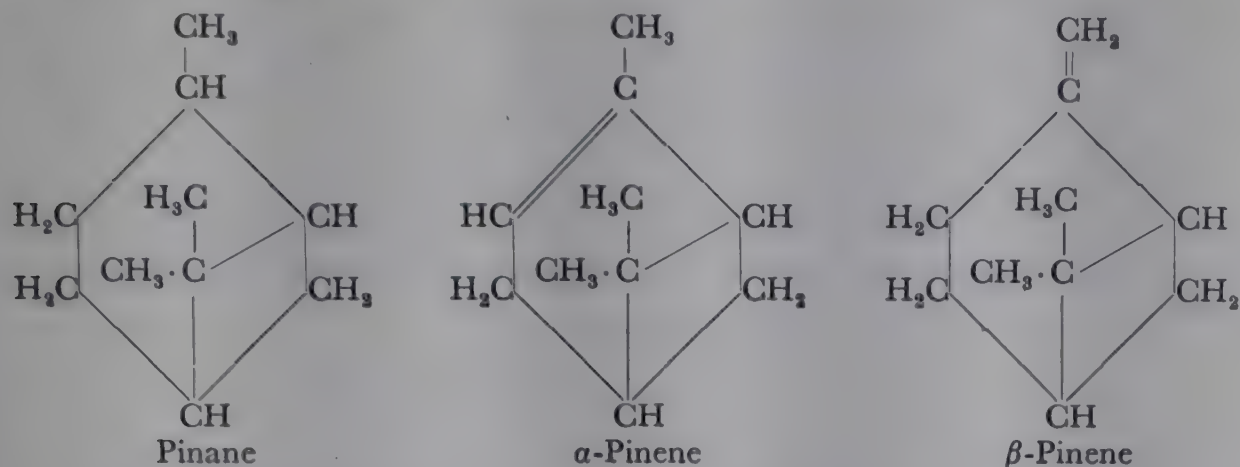


d- Δ^3 -CARENE, a derivative of carane, occurs naturally in Indian turpentine oil from *Pinus longifolia* (the numbering of the carbon atoms in this compound is that usually adopted in the literature).

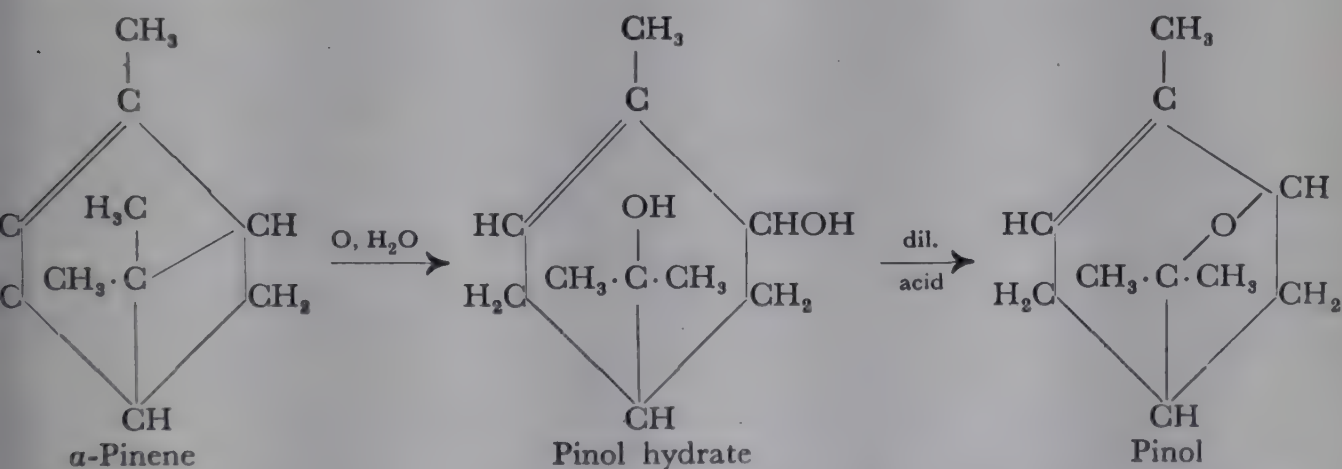
Pinane group

Pinane itself has not yet been found naturally, but the two unsaturated hydrocarbons, α -pinene and β -pinene, are the chief constituents of the "turpentine oils". By the term "turpentine oils" is understood the steam-volatile fraction of the resinous exudation of various species of *Pinus*.

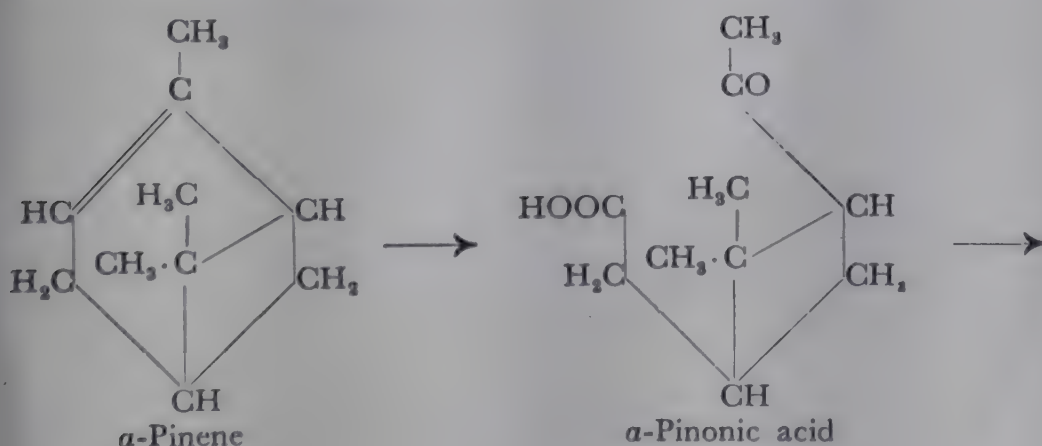
α -Pinene predominates in the mixture of pinenes. It occurs in a dextro-, levorotatory, and inactive form. Pure α -pinene, purified by means of pinene nitrosochloride, boils at 155–156°. The highest observed specific rotation is + 53.7°. The boiling point of β -pinene is 162–163°.

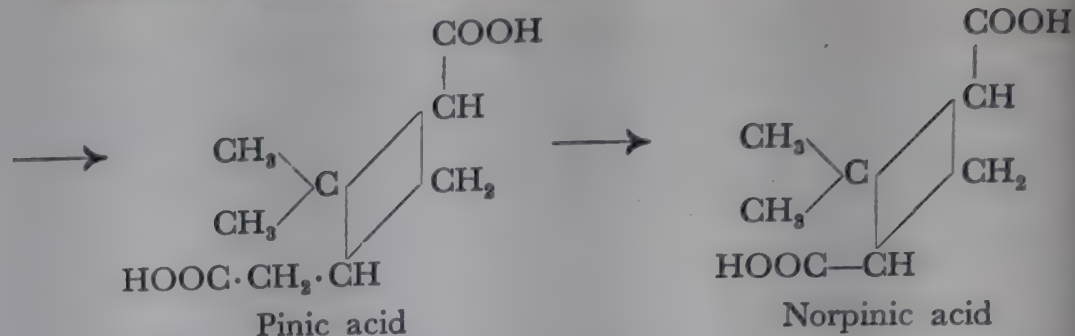


α -Pinene is autoxidizable. It takes up oxygen from the air, and forms first peroxides, which then break down into simpler oxides, giving up some of the oxygen. If moisture is also present, *pinol hydrate* (sobrerol) is formed as a product of the oxidation, and separates as crystals from the turpentine oils. If pinol hydrate is boiled with acids, it is converted into *pinol*, which belongs to the same type as *cineole* (see p. 681). Wagner has put forward the following formulation of these reactions:



The oxidation of α -pinene with permanganate leads to pinonic acid, pinic acid, and norpinic acid:

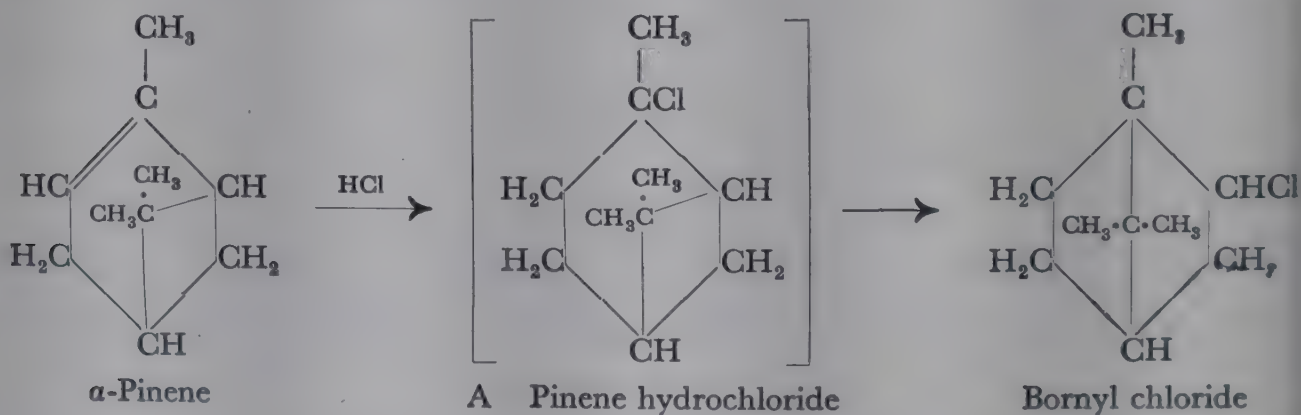




On treatment with dilute mineral acids α -pinene is hydrolysed, the *cyclo*-butane ring being ruptured, first to α -terpineol, and finally to terpin hydrate. If α -pinene is heated to 340–350° there is a rupture of both rings, and an interesting isomerization to *alloöcimene* takes place:

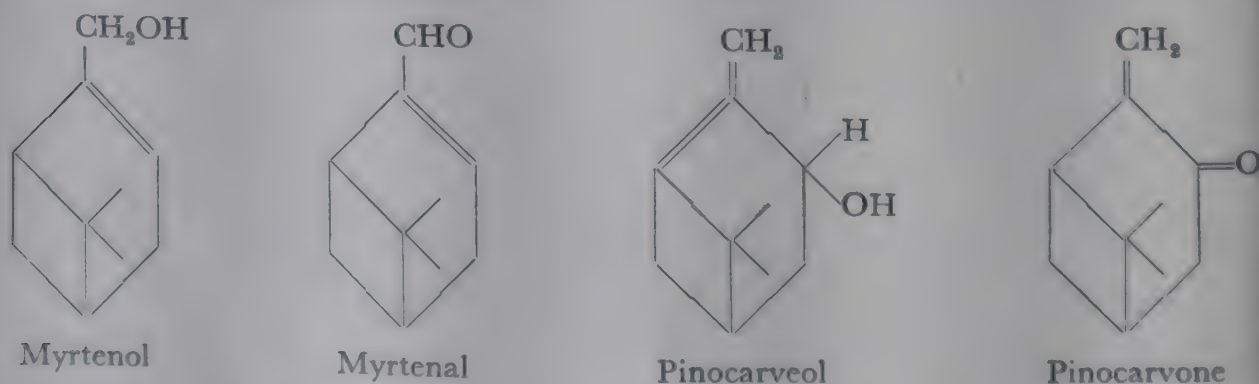


Of considerable, and also practical, interest (synthesis of camphor!) is the addition of dry hydrogen chloride and other anhydrous acids to α -pinene. Simultaneously with, or immediately after, the addition of these compounds across the ethylenic linkage in α -pinene, a rearrangement occurs, so that the carbon bridge, which in pinene united the ring carbon atoms 2 and 4, is now displaced to link the 1 and 4 positions. The process is thus a transformation of the pinane ring system into that of camphane:

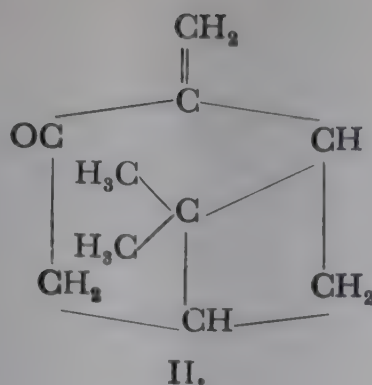
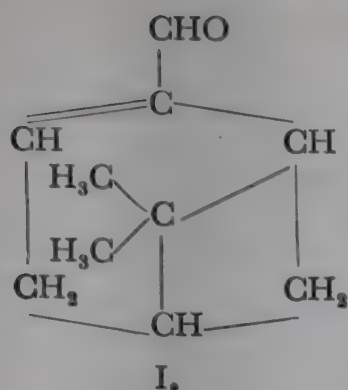


Meerwein and Aschan have obtained true pinene hydrochloride (A) at low temperatures. Even at room temperature, however, rearrangement into bornyl chloride occurs.

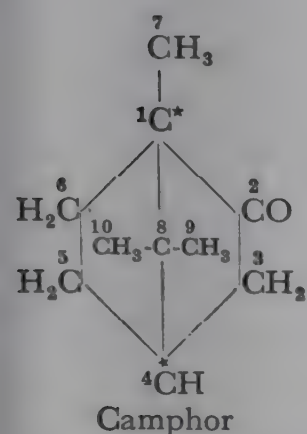
Some derivatives of α -pinene, containing oxygen, have been found in essential oils. Thus, Spanish eucalyptus oil contains the alcohols myrtenol and pinocarveol, the aldehyde myrtenal, and the ketone pinocarvone:



β -Pinene is oxidized by selenium dioxide to myrtenal (I) and pinocarvone (II):



Camphane group



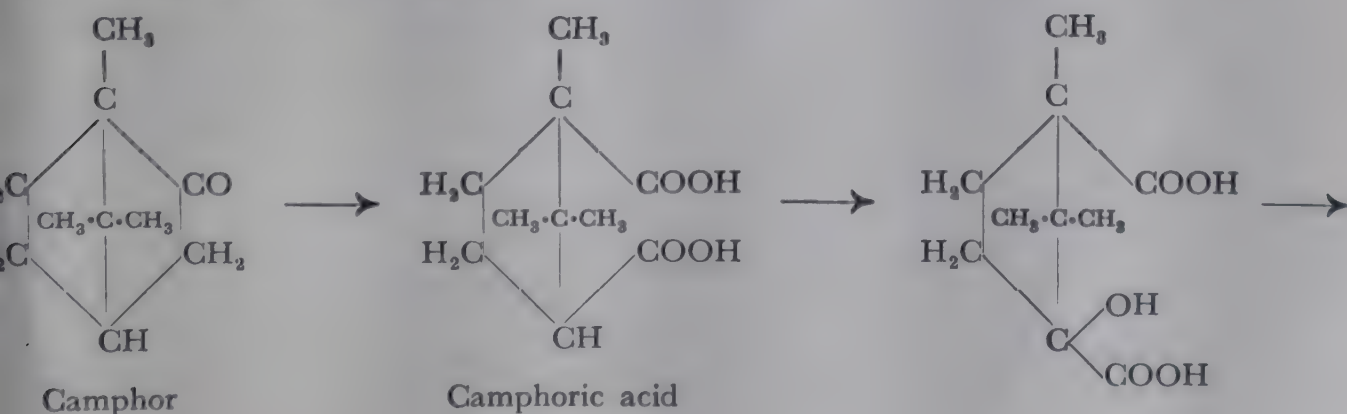
The most important compound of this group is *camphor*, of which the dextrorotatory form is a main constituent of camphor oil, which is derived from the camphor tree (*Cinnamomum camphora*). *d*-Camphor is also called *Japan camphor*. The *l*-form, *Matricaria camphor*, is much more rarely met with, being found in some essential oils. These two active modifications are antipodes. Camphor possesses two asymmetric carbon atoms. Of the four isomerides theoretically possible, up to the present it has only been possible to prepare the two enantiomorphous *cis*-forms, the two camphors in which

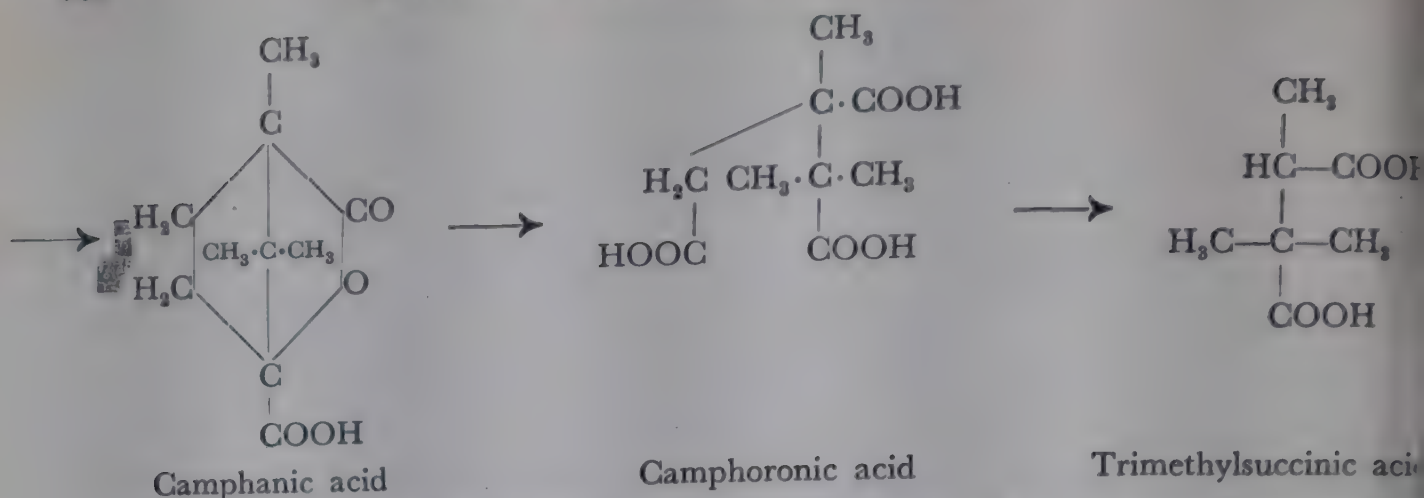
the one *cyclopentane* ring in the molecule is in the *trans*-position to the other being apparently too unstable to exist owing to the strain imposed on the molecule by such a distortion.

Japan camphor melts at 178–179°, and has a specific rotation, $[\alpha]_D = +44.2^\circ$, in alcohol. It has a characteristic strong odour. It is an important technical product, being used as an addition to cellulose nitrates and acetates in the celluloid industry, for the manufacture of smokeless powder, and for medicinal purposes. Its use in medicine is chiefly for the stimulation of the muscles of the heart, and as a disinfectant.

The constitution of camphor, which was first correctly recognized by *Bredt*, was established by oxidative degradation, and by its total synthesis.

Oxidation with nitric acid leads to *camphoric acid*; this can be further oxidized to *camphanic acid*, and *camphoronic acid*, and finally to trimethylsuccinic acid (*Bredt*, *Perkin* and *Thorpe*):





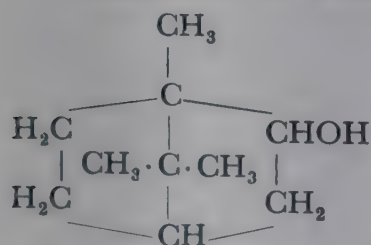
Camphoric acid has two asymmetric carbon atoms. The four optical isomers thus required are known. There are *d*- and *l*-camphoric acid (m.p. 187°; $[\alpha]_D = \pm 49.8^\circ$ in alcohol), which are antipodes, and in which the two carboxyl groups are in the *cis*-position. They readily form camphoric anhydrides (m.p. 221°) on dehydration. In addition, there are *d*- and *l*-isocamphoric acid (m.p. 171°; $[\alpha]_D = \pm 48^\circ$), the carboxyl groups of which are in the *trans*-position. They do not form anhydrides.

By the total synthesis of camphoric acid, carried out by Komppa, not only was the constitution of the acid confirmed, but the total synthesis of camphor was made possible, as it had already been found possible (Haller) to convert camphoric acid into camphor.

Komppa's synthesis of camphoric acid started with oxalic ester and β,β -dimethylglutaric ester, and was carried out as shown on p. 701.

A large number of investigations has been carried out on the chemical reactions of camphor. Only a few of these can be mentioned here.

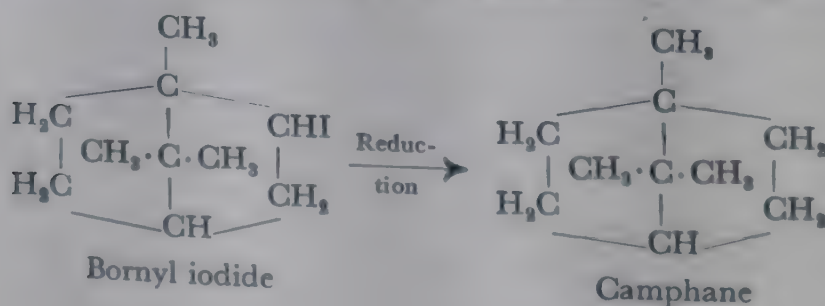
Reduction of *d*-camphor gives *d*-borneol and in addition some *l*-isoborneol.

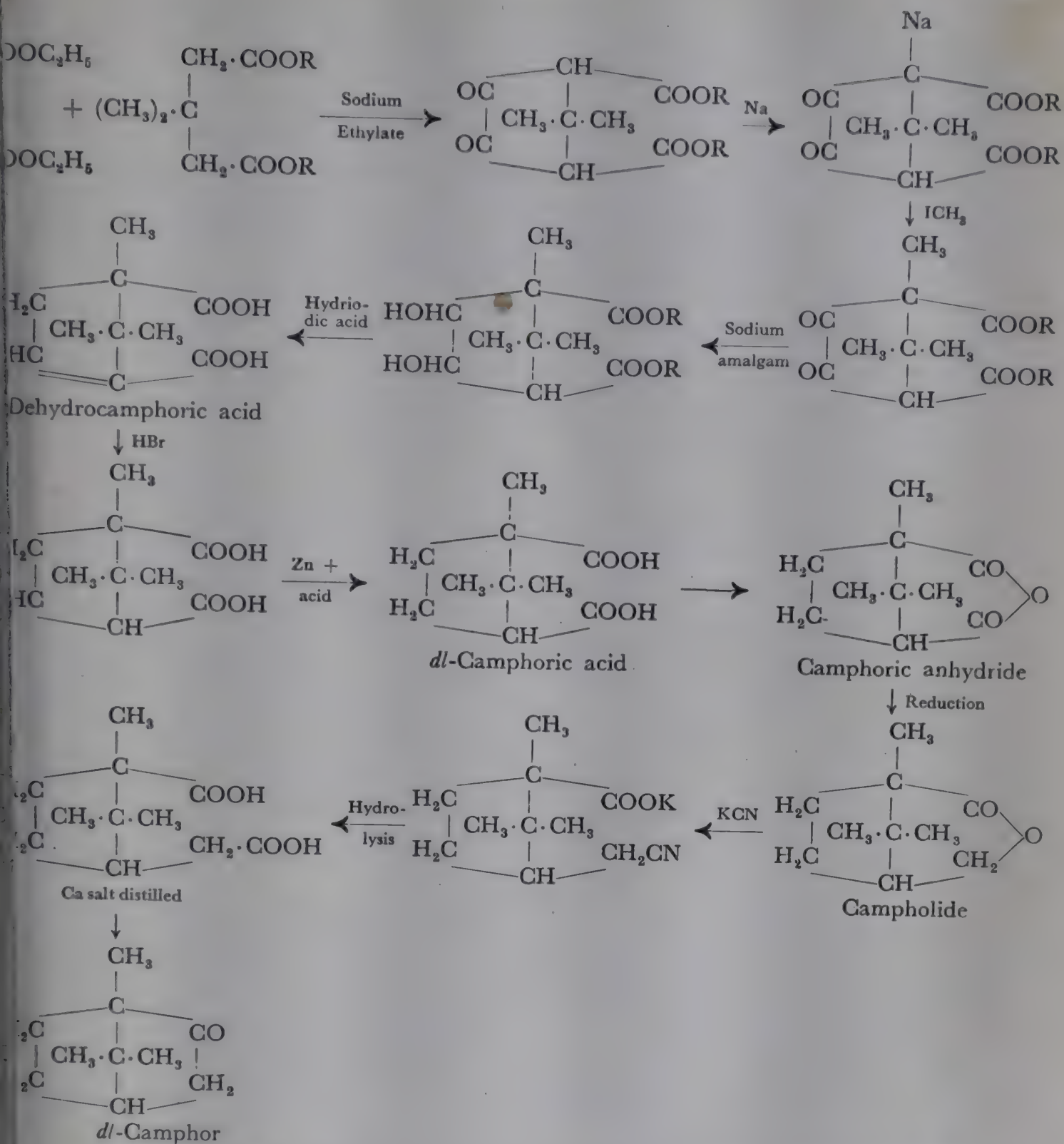


l-Camphor gives, of course, the corresponding antipodes, *l*-borneol and *d*-isoborneol. *d*-Borneol, also known as Borneo camphor, occurs in numerous essential oils, both in the free state and as esters (e.g. oil of lavender, oil of rosemary, and spike oil; *d*-borneol from *Dryobalanops camphora* is almost pure). It melts at 202–203°, boils at 214°, and has $[\alpha]_D = +37.4^\circ$. Its constitution is given by the accompanying formula.

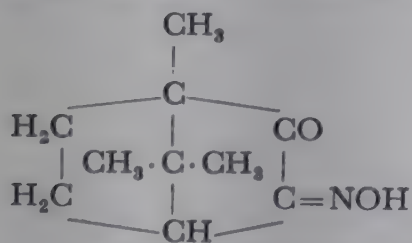
The antipode, *l*-borneol or Ngai camphor, comes mainly from *Blumea balsamifera* and from valerian oil.

Bornyl chloride (pinene hydrochloride) is of practical importance. Its formation by the addition of hydrogen chloride to α -pinene has already been mentioned. Reduction of active bornyl iodide gives the optically inactive hydrocarbon camphane, whose inactivity points to a symmetrical structure, and this is important in connection with the elucidation of the constitution of camphene derivatives:

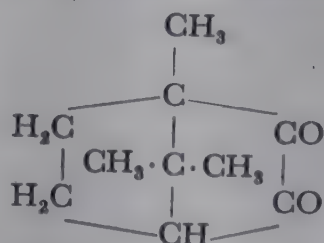




The reaction of camphor with amyl nitrite and alcoholates may be mentioned. It gives isonitrosocamphor, which on hydrolysis yields the yellow camphorquinone.



Isonitrosocamphor

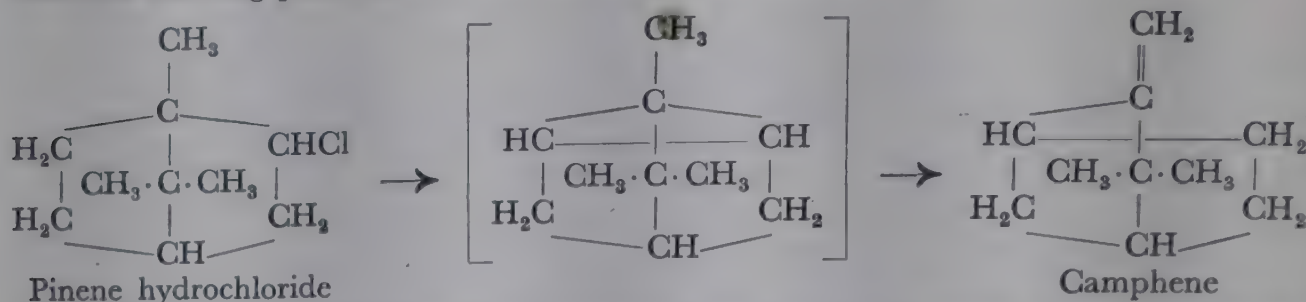


Camphorquinone

Camphorsulphonic acid and bromocamphorsulphonic acid, being readily accessible optically active acids, are frequently used for the resolution of racemic bases into their optically active forms.

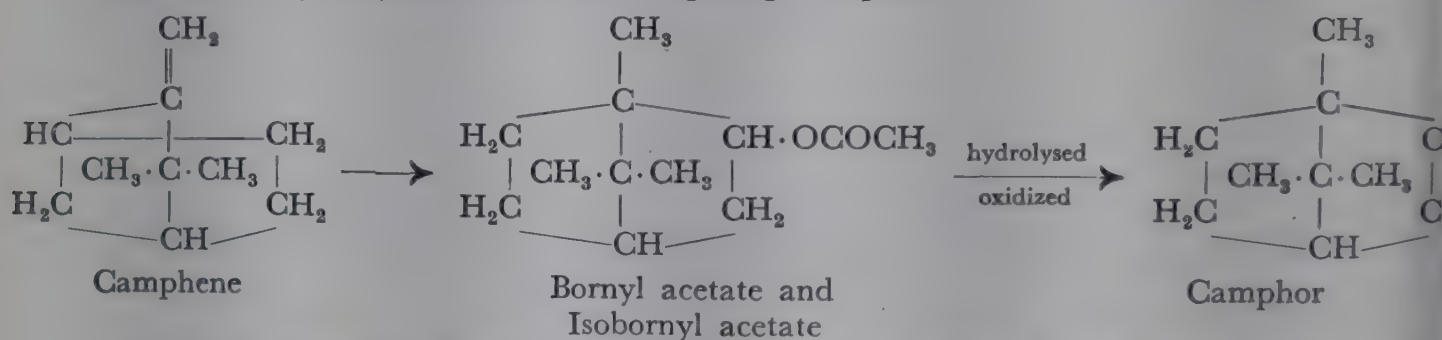
The technical importance attaching to camphor, for the manufacture of celluloid, in recent years has led to its artificial preparation from cheap starting materials. The various technical methods of manufacture all start with oil of turpentine or its chief constituent α -pinene. The following processes may be mentioned:

1. Bornyl chloride (pinene hydrochloride) which is obtained from α -pinene by addition of hydrogen chloride, is converted into *camphene* by heating with alkalis or salts of fatty acids or similar substances. This unsaturated hydrocarbon is the essential starting point for the technical syntheses of camphor:



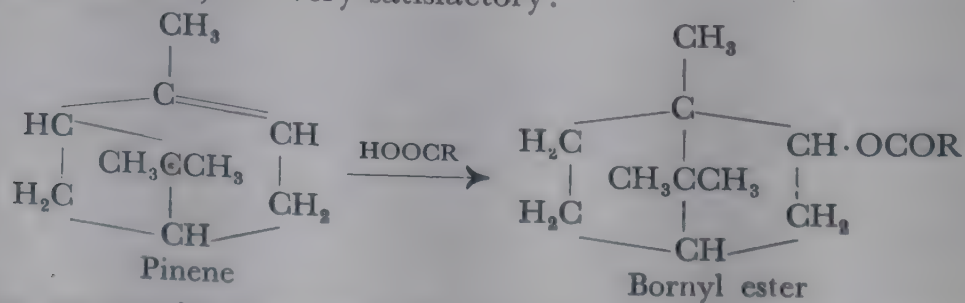
The conversion of pinene into camphene may also be brought about by heating pinene in the presence of catalysts (borophosphoric acid, magnesium or nickel sulphates).

Acetic acid is added on to camphene by means of a mixture of glacial acetic acid and sulphuric acid, and the acetates of isborneol and (little) borneol obtained are hydrolysed and oxidized, giving camphor:

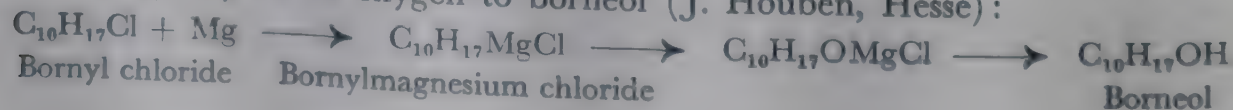


The camphene is mostly, however, directly oxidized by chromic acid to camphor. In this case, too, borneol and isborneol probably occur as intermediate stages by the addition of water to camphene, and they are then oxidized to camphor.

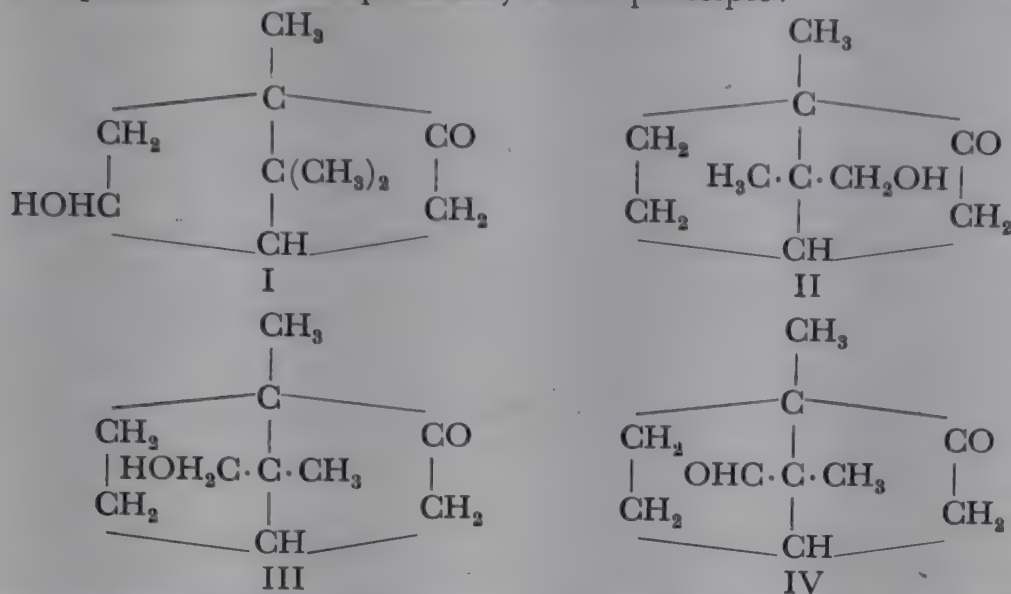
2. It is also possible to add organic acids (e.g. oxalic, acetic, and salicylic acids) directly to pinene, giving esters of borneol in one operation. These are then converted into camphor by the method described above. The yields of these processes are, however, not very satisfactory:



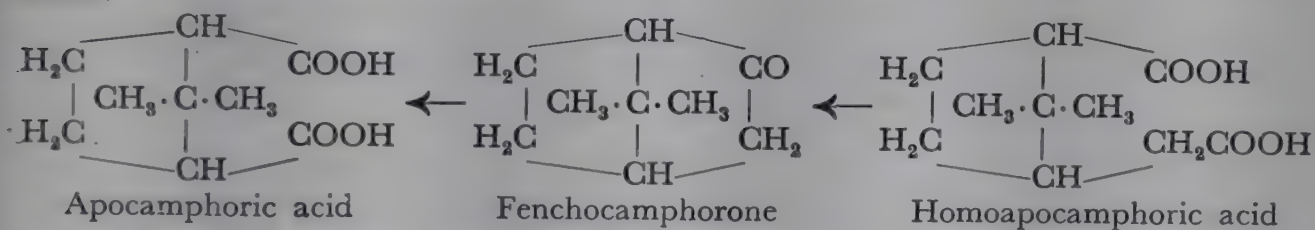
3. For preparative purposes (the process cannot be used technically on account of the high cost of materials), camphor can be synthesized by first converting pinene hydrochloride into the magnesium compound, which is then oxidized by dry air or oxygen to borneol (J. Houben, Hesse):



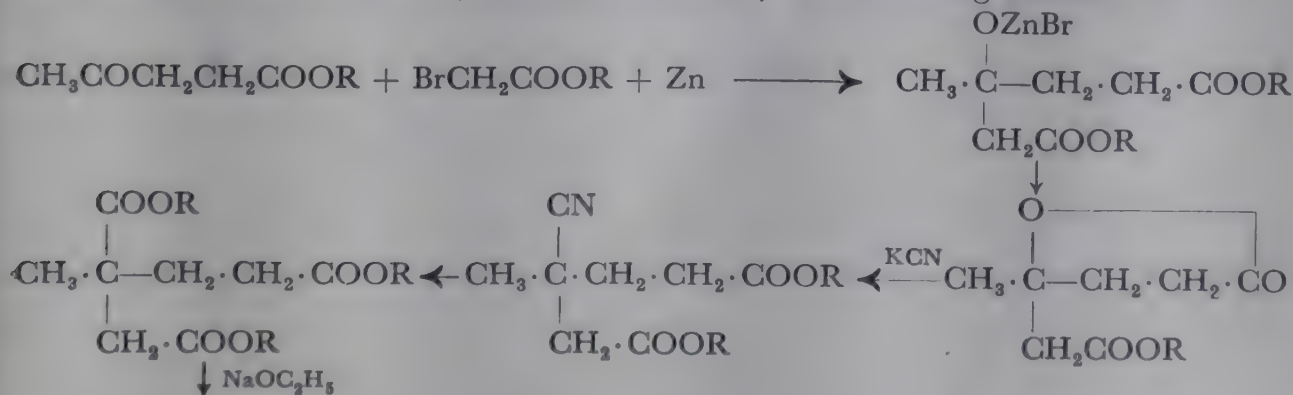
Animals to which camphor has been administered, detoxicate it by converting it into hydroxy-derivatives, which are largely excreted in the urine conjugated with glucuronic acid. These hydroxy-derivatives were recognized as 5-hydroxycamphor (formula I), 3-hydroxycamphor, and *cis*- and *trans*- π -hydroxycamphor (II and III) (Asahina, Ishidate). *Trans*- π -hydroxycamphor then undergoes partly a further oxidation to *trans*- π -ketocamphor or *vitacamphor* (IV), which, according to Tamura, represents the therapeutically active principle:



α -Fenchocamphorone is a lower homologue of camphor which has not yet been found in nature. Its constitution has been determined by Wallach by its oxidation to apocamphoric acid, and by Komppa by its synthesis from homoapocamphoric acid (see p. 640). Both degradation and synthesis are based on the corresponding reactions in the camphor series:



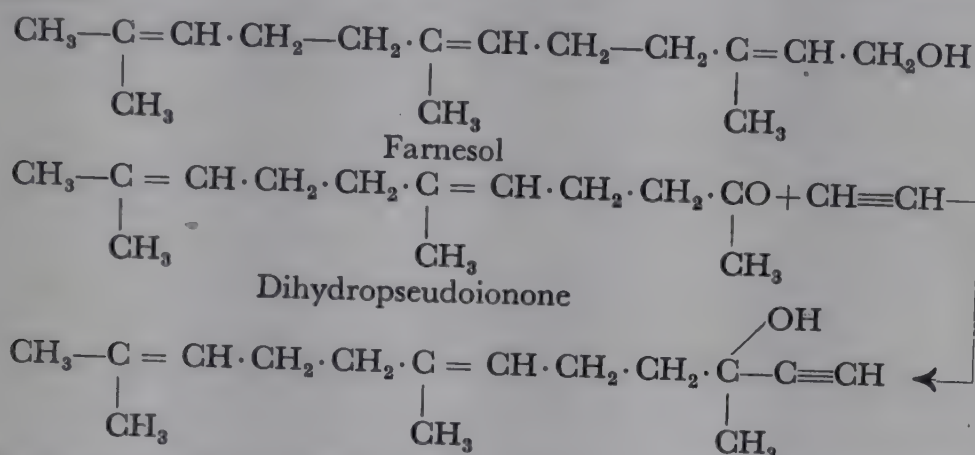
Fenchones. *Fenchone* is isomeric with camphor, but is distinguished from it by its greater resistance to oxidation. Its *d*-form occurs in fennel oil, and the *l*-form in oil of thuja. It boils at 192–193°, and melts at 5–6°. The constitution of fenchone was unequivocally established only by the synthesis of the ketone (Ruzicka), before which various formulæ had been proposed for the substance. Lævulinic ester, bromoacetic ester, and zinc are the starting materials, and the course of the synthesis is shown by the following scheme:



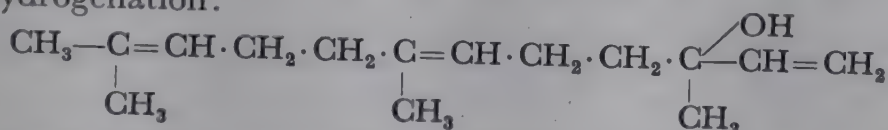
penes we meet substances with open chains, and others with one, two, or three ring systems in the molecule. The distribution of sesquiterpenes in essential oils and plant juices is very considerable.

According to a very useful hypothesis (Ruzicka) many sesquiterpenes, and polyterpenes up to rubber, may be regarded as polymerization products of isoprene, $\text{CH}_2=\text{C}(\text{CH}_3)\cdot\text{CH}=\text{CH}_2$. They are made up of several isoprene molecules added to each other in various ways. This hypothesis had proved correct for most members of these groups, of which the carbon skeleton is known.

ALIPHATIC SESQUITERPENES. Amongst these, the two alcohols of the formula $\text{C}_{15}\text{H}_{26}\text{O}$, *farnesol* and *nerolidol*, are important as perfumes. The first compound of the series of sesquiterpenes of which the constitution was elucidated (Kerschbaum) was farnesol, a constituent of many odoriferous oils (those of lilies of the valley, lime flowers, musk seeds, etc.). The oxime of the aldehyde obtained by oxidizing farnesol gives a nitrile on splitting off water. On hydrolysis this gives in addition to the corresponding acid, a ketone two carbon atoms poorer, $\text{C}_{13}\text{H}_{22}\text{O}$, dihydropseudoionone. The constitution of the latter is definitely known from its synthesis (ketonic hydrolysis of geranylacetoacetic ester). Farnesol can be synthesized again from this ketone:



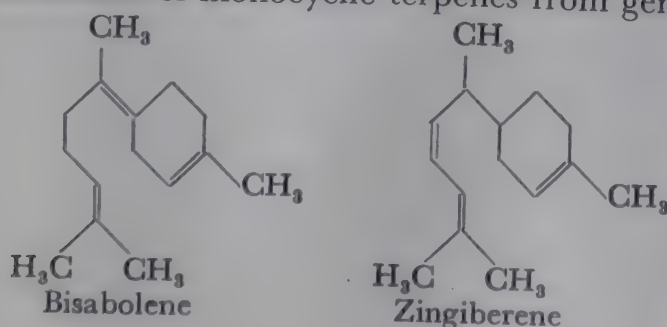
The product obtained by condensation with sodium acetylide gives *dl*-nerolidol on partial hydrogenation:



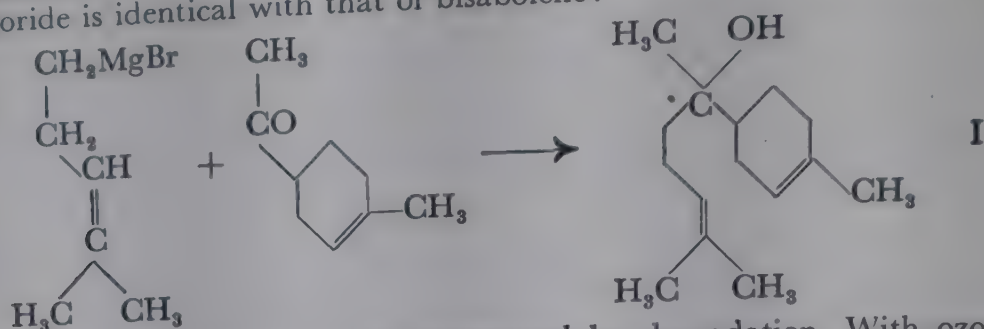
This alcohol occurs in the optically active form in balsam of Peru. On treatment with acetic anhydride, rearrangement to farnesol takes place (Ruzicka).

The investigations of Ruzicka, in particular, have been of special value in elucidating the constitution of cyclic sesquiterpenes.

MONOCYCLIC SESQUITERPENES. The most important member of this sub-group, *bisabolene* (oil of lemons, pine needle oil, etc.), can be obtained synthetically, e.g. by the moderated action of strong acids on nerolidol or farnesol. This reaction is analogous to the formation of monocyclic terpenes from geraniol or linalool:

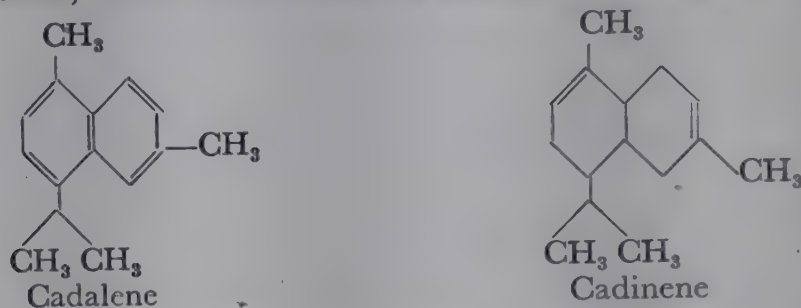


A further synthesis which confirms the foregoing formula for bisabolene depends on the reaction between 2-methylpentenyl-(2)-magnesium bromide-(5) with 1-methyl-4-acetylcyclohexene-(1) which leads to the alcohol bisabolol (I), of which the crystalline trihydrochloride is identical with that of bisabolene:



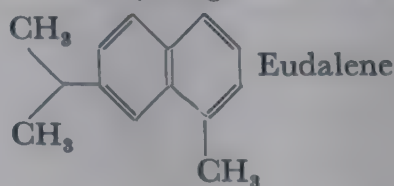
The formula of bisabolene is also supported by degradation. With ozone it gives acetone and lævulinic acid. On catalytic hydrogenation a tetrahydrobisabolene is obtained which on ozonolysis gives 4-methylcyclohexanone (I) and methyl isohexyl ketone. A second monocyclic sesquiterpene, contained in oil of ginger, is *zingiberene*; it differs from bisabolene only in the position of one double bond.

BICYCLIC SESQUITERPENES. A series of bicyclic sesquiterpenes amongst which the most important is *cadinene*, $\text{C}_{15}\text{H}_{24}$, has been dehydrogenated by heating with sulphur or selenium, or catalytically, to *cadalene*, $\text{C}_{15}\text{H}_{18}$, 1:6-dimethyl-4-isopropylnaphthalene, whose constitution is known by synthesis:

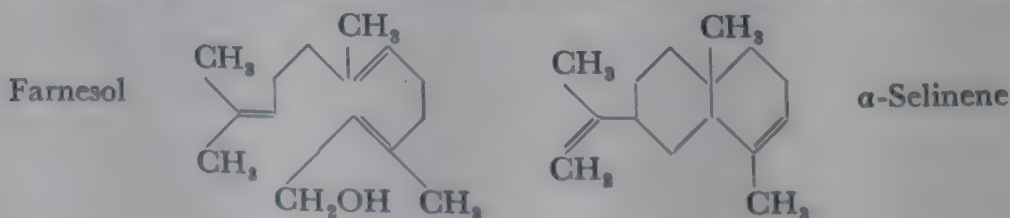


It follows that the above-mentioned sesquiterpenes have the carbon skeleton of cadalene and have the structure of hexahydro-1:6-dimethyl-4-isopropylnaphthalenes. The differences between them are due to the different positions of the double bonds, and different steric structure. It is noteworthy that the above-mentioned two monocyclic sesquiterpenes give hexahydrocadalenes on energetic treatment with strong acids, in which the positions of the two double bonds have not yet been determined. The hexahydrocadalenes can thus be regarded as condensation products of the aliphatic sesquiterpenes.

Another group of bicyclic sesquiterpenes, such as *selinene* (oil of celery) and *eudesmol* (eucalyptus oil) give *eudalene*, $\text{C}_{14}\text{H}_{16}$, on heating with sulphur. The constitution of eudalene is known by degradation and synthesis. It is 1-methyl-7-isopropylnaphthalene:

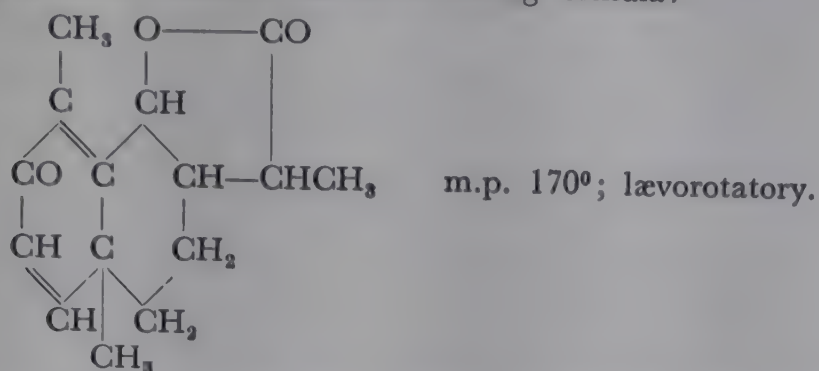


This group of sesquiterpenes appears also to be derived from the aliphatic sesquiterpene chain, as a comparison of the formulæ of farnesol and selinene shows:

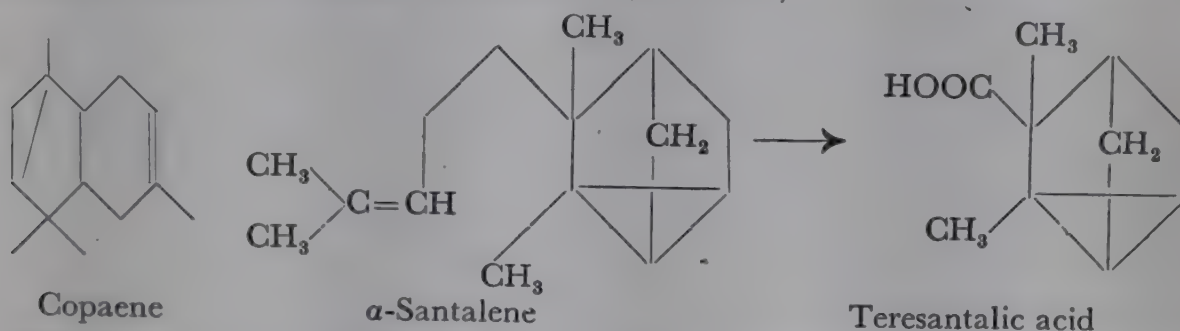


On dehydrogenation of these sesquiterpenes the methyl group at the junction of the two rings is eliminated. There are, however, also some bicyclic terpenes which do not contain a hydrogenated naphthalene ring (e.g. caryophyllene, in which probably a four- and a seven-membered carbon ring are ortho-condensed).

SANTONIN, $C_{15}H_{18}O_3$, a constituent and the active principle of the so-called wormseed (*Flores cinæ*) is to be regarded as an oxygen-containing derivative of a bicyclic sesquiterpene. According to G. R. Cleme it has the following formula:

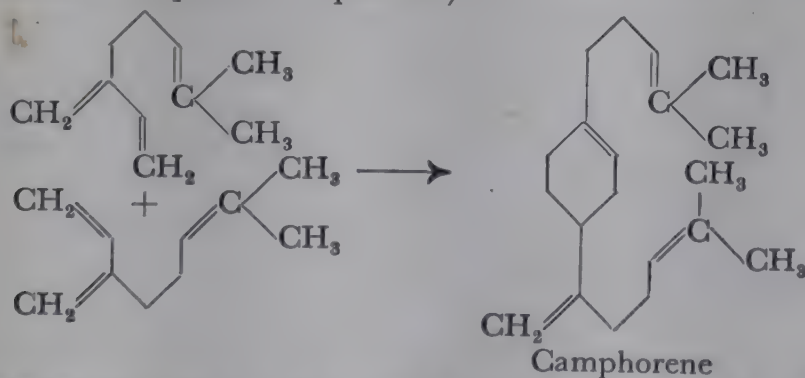


TRICYCLIC SESQUITERPENES. Also members of this class are known which are derived from cadalene and eudalene. Amongst the former is *copaene* (African copaiba balsam), which gives cadinene dihydrochloride with hydrogen chloride. Amongst the latter is α -santalene (East Indian sandalwood oil), which gives teresantalic acid by stepwise degradation (Semmler):



The constitution of other important tricyclic sesquiterpenes, such as *cedrene* and *gurjunene* is still not definitely known.

Progress has recently been made in the investigation of the diterpenes, $C_{20}H_{32}$, and the triterpenes, $C_{30}H_{48}$. These hydrocarbons and their oxygen derivatives occur mainly in vegetable resins and balsams. The constitution of *camphorene*, $C_{20}H_{32}$ (oil of camphor), is fully known. The substance is also formed by the polymerization of myrcene (analogous to the polymerization of isoprene to dipentene):

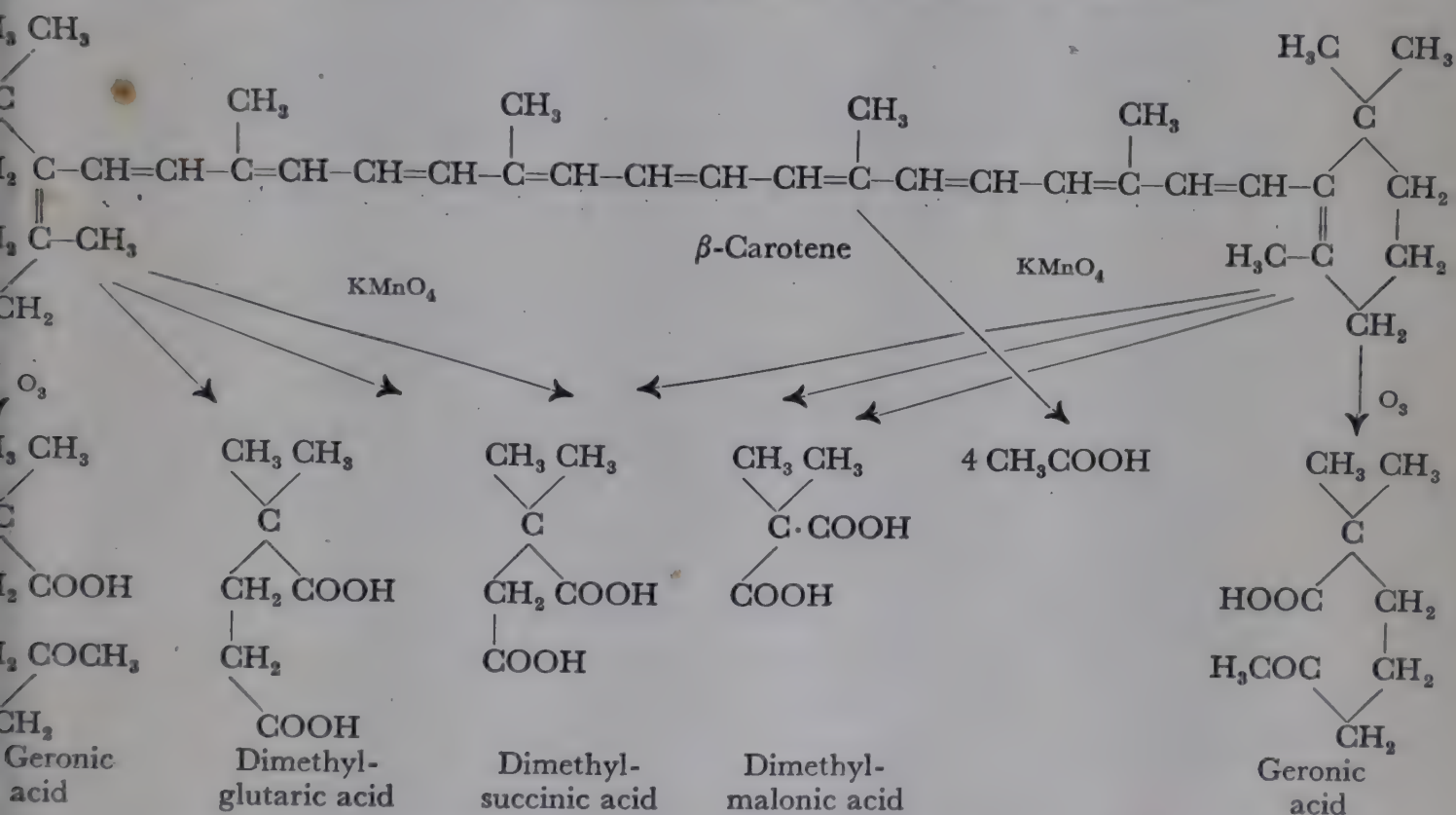


The most important member of this class is abietic acid, $C_{20}H_{30}O_2$, the carboxylic acid of a diterpene which forms the chief constituent of colophony resin, and can be obtained from the latter by distillation. On heating with sulphur or with palladium-charcoal it is degraded to retene (see p. 412), i.e. 1-methyl-7-isopropylphenanthrene. 1:3-Dimethylcyclohexan-2-one is formed in small quantities by the oxidation of abietic acid with potassium permanganate. The most probable formula of abietic acid is that of a dimethylisopropyldecahydrophenanthrenecarboxylic acid, containing two double bonds in the

Isomeric with lycopene is **carotene**, $C_{40}H_{56}$, which Wackenroder isolated (1831), as the first carotenoid pigment, from the yellow carrot. It is one of the most widely spread natural pigments, occurring with chlorophyll and xanthophyll (see p. 710) always in green leaves, and also in numerous flowers and fruits. It is also contained in the animal organism (fat, milk, blood serum, etc.). Its hydrocarbon nature was recognized by Arnaud, and its molecular formula, $C_{40}H_{56}$, was determined by Willstätter.

More recent investigations have shown that the pigment of the carrot occurs as three isomerides, which are distinguished as α -, β -, and γ -carotene. The difference between them lies in the position of the double bonds. α -Carotene is optically active (dextrorotatory); β - and γ -carotene are optically inactive.

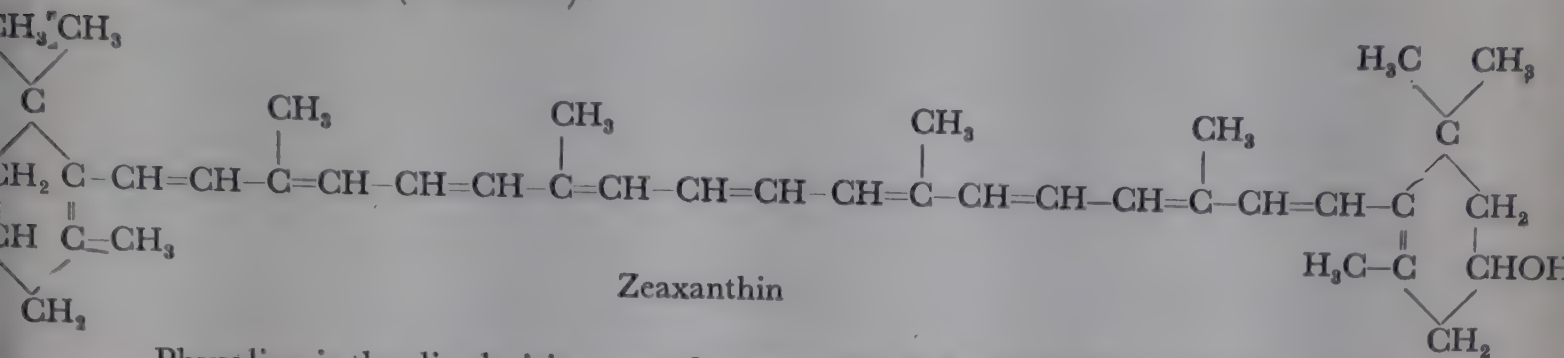
When catalytically hydrogenated, β -carotene takes up 11 molecules of hydrogen (Zechmeister). It therefore contains 11 carbon double bonds. Its constitution has been arrived at by oxidative degradation. The action of potassium permanganate leads to 4 molecules of acetic acid, 1:1-dimethylglutaric acid, 1:1-dimethylsuccinic acid, and dimethylmalonic acid. With ozone it gives geronic acid. These results are taken into account by the following formulation, which regards β -carotene as a cyclization product of lycopene (P. Karrer):



Carotene is also autoxidizable. H. von Euler has found it to be an essential growth-promoting factor in animals and man. The animal organism converts carotene into the fat-soluble growth-factor vitamin A (see p. 728). The latter is a derivative of β -carotene which is produced by fission of carotene.

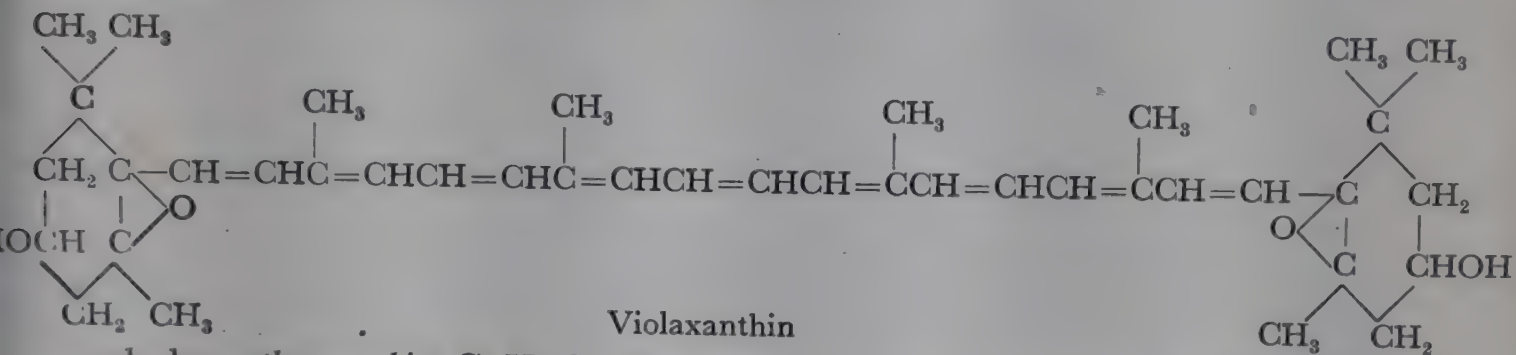
α -Carotene differs from the β -isomeride in having one double bond in a different position. Its molecule ends on the one side with the same carbon ring which occurs twice in β -carotene (the β -ionone ring), but at the other end of the α -carotene molecule there is an α -ionone ring, which differs from the β -ionone ring in the position of the double bond (between carbon atoms 3' and 4'). The oxidation of α -carotene thus leads to geronic acid and the isomeric isogeronic acid:

permanganate. The positions of the hydroxyl groups in the carbon rings must therefore be such that the formation of the latter acid is not possible. This fact is taken into account in the following formulation, which is also confirmed by other observations (P. Karrer):

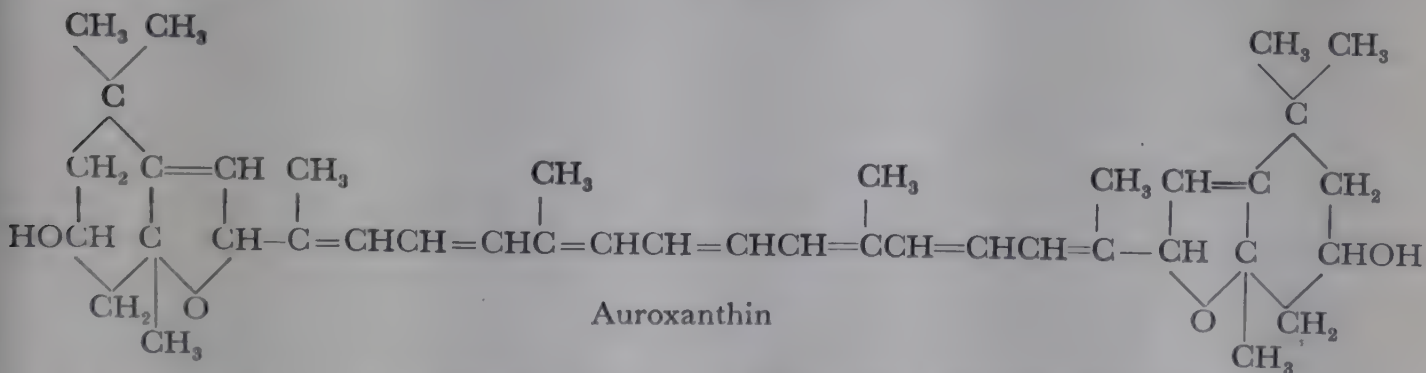


Physalien is the dipalmitic ester of zeaxanthin. It has been found in the calyx and fruit of *Physalis*, in the fruits of *Evonymus europæus*, *Hippophæ rhamnoides*, species of *Lycium*, etc.

Some natural carotenoids richer in oxygen have been recognized as *epoxides* by P. Karrer, e.g. *violaxanthin*, $C_{40}H_{56}O_4$, a zeaxanthin di-epoxide of the following structure:



and also *antheraxanthin*, $C_{40}H_{56}O_3$, the corresponding mono-epoxide derived from zeaxanthin, and *xanthophyll mono-epoxide*, $C_{40}H_{56}O_3$ (with the oxide oxygen on the β -ionone ring). These compounds may also be prepared by partial synthesis. By the action of extremely dilute acids they rearrange to oxides of a furanoid structure, which also occur in the vegetable kingdom. The furanoid rearrangement-product of violaxanthin is *auroxanthin*, $C_{40}H_{56}O_4$ (e.g. from the yellow blossoms of *Viola tricolor*):



In a similar way, *mutatoxanthin*, $C_{40}H_{56}O_3$, is produced from *antheraxanthin*, and the furanoid *flavoxanthin*, $C_{40}H_{58}O_3$, from *xanthophyll mono-epoxide*.

FUCOXANTHIN, $C_{40}H_{56}O_6$, is the brown-yellow pigment of brown alga.

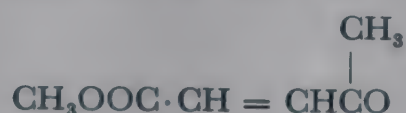
CAPSANTHIN, $C_{40}H_{58}O_3$, is the most important pigment of paprika (Zechmeister). It is ketonic in character, and contains the same carbon skeleton as the carotenes and the phytoxanthins, since it gives the same degradation products (e.g. 1:1-dimethylsuccinic acid). Its constitution was elucidated by Zechmeister.

The two hydrogen atoms taken up are at the two ends of the whole system of conjugated double bonds.

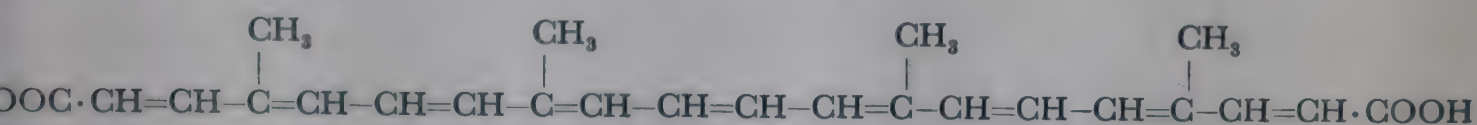
Besides this stable (*trans*-) crocetin, a *cis-trans*-isomeric "labile" crocetin (*cis*-form) is contained in saffron, in a small quantity.

According to R. Kuhn and F. Moewus, crocin is probably the motility factor of the male and female gametes of the green alga *Chlamydomonas eugametos* *f. simplex*, while *cis*- and *trans*-crocetin dimethyl esters are regarded as the attracting and copulating factors of the gametes, the *cis*-compound being preponderantly secreted by the female gametes and the *trans*-isomer by the male gametes, on irradiation with light.

Bixin is the monomethyl ester of norbixin, a dicarboxylic acid homologous with crocetin. Bixin gives β -acetylacrylic ester on ozonolysis:



and on distillation considerable quantities of *m*-xylene. The constitution of bixin has been confirmed by the total synthesis of perhydrobixin methyl ester. The colouring matter of orleans (bixin) thus possesses the formula:



Bixin is a darker red than crocetin, but otherwise has similar properties. It is still used as a drug, in the dyeing of cotton and silk, and especially for colouring butter, margarine, etc.

Sterols. Bile acids. Sex hormones¹

The *sterols*, which are widely distributed in animals and plants, and the related *bile acids*, present in bile, have a very complex structure. Their molecules contain four hydrogenated carbon rings, of which three are *cyclohexane* rings. Sterols and bile acids therefore belong to the polycyclic polyterpenes and camphors as regards their constitution, and it is not improbable that they are also genetically connected with simpler terpene compounds.

Sterols. The sterols occurring in animals are called *zoosterols*, and those occurring in plants *phytosterols*. Both groups comprise many members and are related to each other.

The best-investigated animal sterol is *cholesterol*, $\text{C}_{27}\text{H}_{45}\text{OH}$, which, partly in the form of esters, occurs in almost all organs, but particularly abundantly in the brain and nerves. Gallstones, which contain cholesterol as their chief constituent, are a suitable starting material for its preparation.

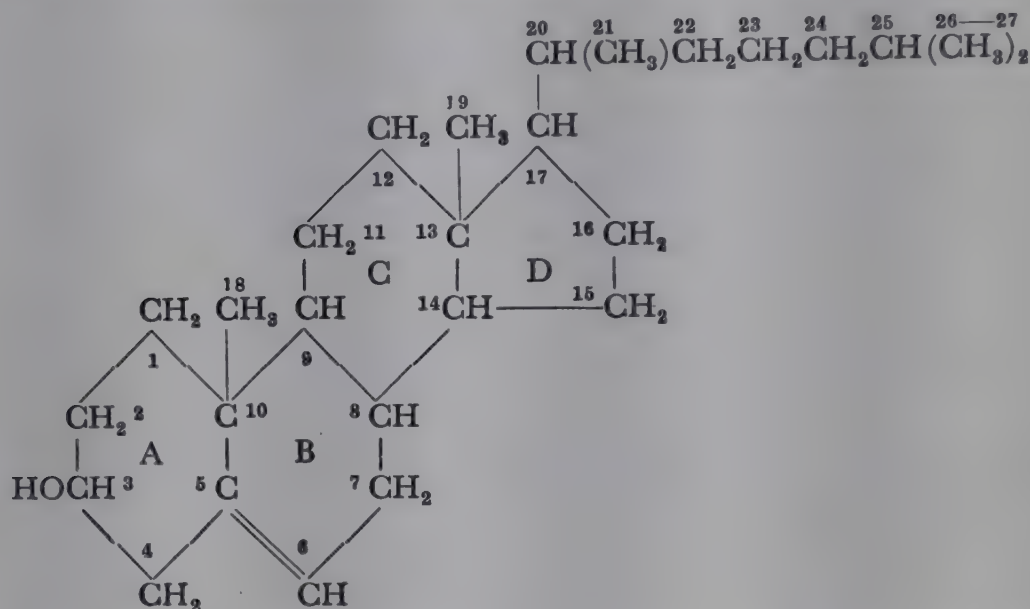
Cholesterol is a well-crystallized, optically active, monohydric alcohol (m.p. 148° , $[\alpha]_D = -36^\circ$ in chloroform), and possesses one double bond

¹ Elsevier's *Encyclopædia of Organic Chemistry*, Vol. 14, Amsterdam, (1940).

in the molecule, which can be detected by the action of bromine. On hydrogenation it takes up two atoms of hydrogen. The hydroxyl group is secondary since the dehydrogenation of cholesterol with copper oxide at 300° gives rise to a ketone, *cholestenone*, $C_{27}H_{44}O$. Reduction of cholestenone gives rise to the saturated hydrocarbon $C_{27}H_{48}$, *cholestane*.

These facts, especially the molecular formula of the saturated hydrocarbon *cholestane*, allow of the conclusion that cholesterol has 4 carbon rings in its molecule.

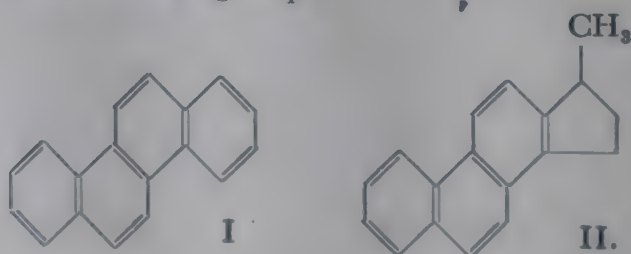
The work of Windaus and Wieland especially has thrown light on the constitution of this complex substance. The constitutional formula generally accepted to-day is based on a fortunate idea of O. Rosenheim, which was modified by Wieland. The Rosenheim-Wieland structural formula is as follows:



The investigation of the constitution of this complex alcohol, which has been carried out in close connection with that of the bile acids, cannot be given in detail here. Some idea of the nature of the side chain was given, for example, from a fission product which is formed by oxidation of cholesteryl acetate, and which has been recognized as 2-methylheptanone-(6):

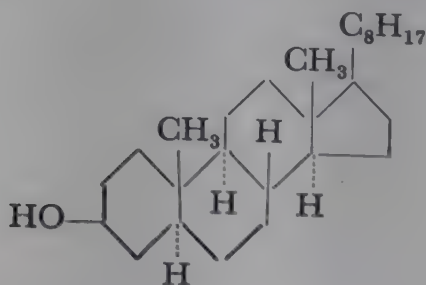


The dehydrogenation of cholesterol with palladium-charcoal led to chrysene (I), whilst distillation with zinc dust gave chrysene and naphthalene. Particularly important is the hydrocarbon $C_{18}H_{16}$, found by Diels as a product of the dehydrogenation of cholesterol, and which is known by synthesis to be a methyl-1:2-cyclopentenophenanthrene of the formula (II). In it the whole cyclic carbon skeleton of cholesterol is retained, and the position of the aliphatic side chain is indicated by the migrated methyl group:

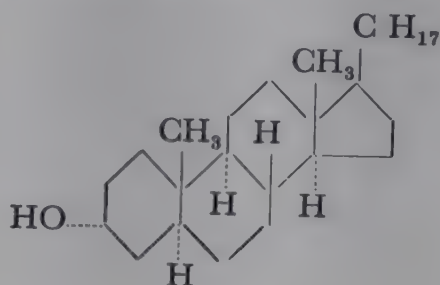


Cholesterol has 8 asymmetric carbon atoms, so that numerous isomerides can be predicted. Such isomers are known, e.g. *epicholesterol*.

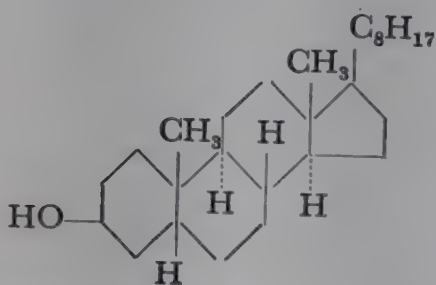
The four condensed rings in cholesterol mean that its dihydro-derivatives, which have a single linkage in place of the double bond, should also exist in *cis-trans* isomeric forms. 8 Compounds are theoretically possible, in which the junctions of the carbon rings are sterically different. A further possibility of isomerism is also to be found in the different spatial arrangement of H and OH at carbon atom 3. Different stereoisomeric dihydrocholesterols are actually known. They are called *dihydrocholesterol*, *epidihydrocholesterol*, *coprosterol*, *epicoprosterol*, and it is thought that they have the following configurations:



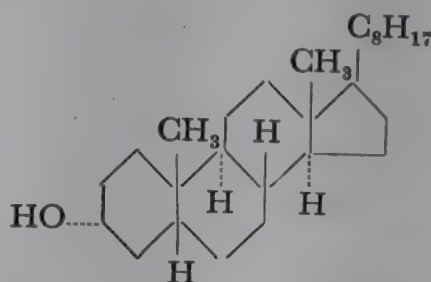
Dihydrocholesterol
trans, trans, trans, trans



Epidihydrocholesterol
cis, trans, trans, trans



Coprosterol *cis, cis, trans, trans*

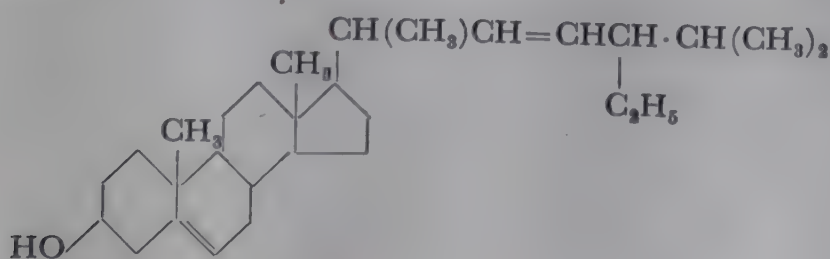


Epicoprosterol *trans, cis, trans, trans*.

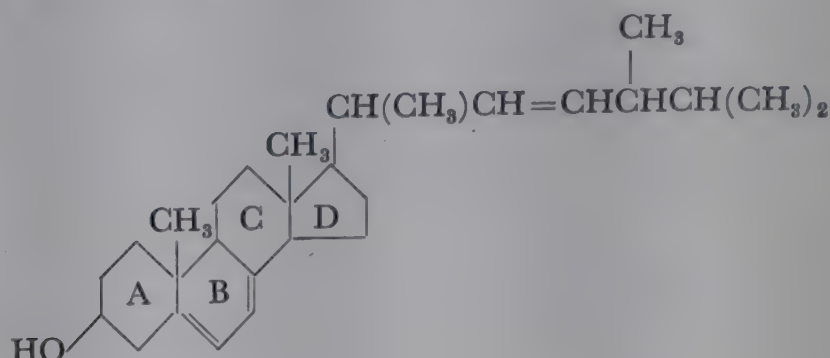
Coprosterol is formed from cholesterol in the intestines by the action of bacteria, and is therefore present in the fæces.

Cholesterol and some other related compounds of this group have the power of forming insoluble precipitates with saponins, which can be used for estimating these substances. Since the saponins act hæmolytically, but not the insoluble cholesterol-saponin addition product, cholesterol inhibits the hæmolytic action of the saponins in the organism.

The plant sterols, *phytosterols*, occur in considerable numbers in nature. *Sitosterol* from the wheat embryo has been given the molecular formula $C_{29}H_{50}O$. It is, like cholesterol, an alcohol, and does not appear to be homogeneous, but a mixture of the isomeric α -, β -, and γ -sitosterols. *Stigmasterol* is a doubly unsaturated alcohol of the formula $C_{29}H_{47}OH$. Fernholz has derived the following structure for the compound:



Ergosterol $C_{28}H_{48}OH$ (contained in yeast, for example) is a compound which has become of outstanding interest, since when exposed to ultra-violet light it is converted into a product which, in minute doses, prevents and cures the disease of rickets in men and animals. It is therefore to be regarded as a factor essential for life and effective in the smallest quantities, a so-called vitamin (see vitamins, p. 727). Ergosterol contains three double bonds, of which two are in the conjugated position in ring B, whilst the third is in the side chain:



Bile acids¹. In the bile of man and many animals certain acids, the so-called bile acids, occur, in addition to cholesterol with which they are structurally closely related, and from which they are probably produced. Thus, human bile contains:

Cholic acid	$C_{26}H_{46}(OH)_3COOH$
Deoxycholic acid	$C_{26}H_{44}(OH)_2COOH$
Anthropodeoxycholic acid	$C_{27}H_{46}(OH)_2COOH$
Lithocholic acid	$C_{26}H_{44}(OH)COOH$,

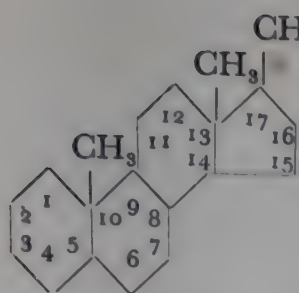
from which cholanic acid, $C_{26}H_{46}COOH$, which contains no alcoholic hydroxyl group, can be obtained by reduction.

Windaus succeeded in converting coprosterol and coprostane into cholanic acid, and thus demonstrated the constitutional connection between the sterols and the bile acids.

The bile acids present in the bile are almost always conjugated with amino-acids, forming peptide-like substances. Thus cholic acid is conjugated with glycine as glycocholic acid, and with taurine as taurocholic acid.

The physiological importance of the bile acids depends in the first place on their power of facilitating the hydrolysis of fats and their digestion. They have the capacity, on the one hand, of emulsifying fats, and thus bringing them into a more favourable condition for enzymic action; on the other hand, some bile acids, such as deoxycholic acid and cholic acid, have the power of combining with substances which are insoluble in water (higher fatty acids, higher ketones, hydrocarbons, etc.) to form high-molecular addition products, which are colloidal soluble in water, and are in this form better suited for enzymic degradation. *Choleic acid*, found in human bile, is, for example, such an addition product, being composed of 8 molecules of deoxycholic acid and 1 molecule of palmitic or stearic acid.

¹ See ELISABETH DANE, *Gallensäuren*, Berlin, (1933).



The constitution of the bile acids, which have been particularly investigated by H. Wieland, is closely connected with that of cholesterol. Cholanolic acid has the same carbon skeleton as cholesterol, but a shorter side chain which contains the carboxyl group.

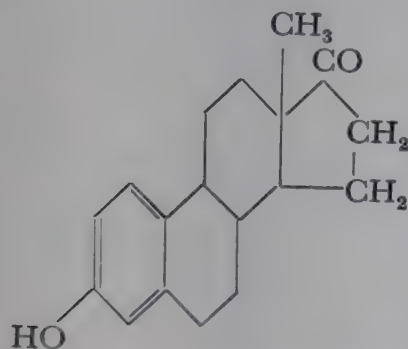
Lithocholic acid is 3-hydroxycholanolic acid, deoxycholic acid is 3:12-dihydroxycholanolic acid, anthropodeoxycholic acid (or chenodeoxycholic acid) is 3:7-dihydroxycholanolic acid, and cholic acid is 3:7:12-trihydroxycholanolic acid.

Further hydroxycholanolic acids have been obtained either artificially, or from the animal body, and in the majority of cases their constitutions are known.

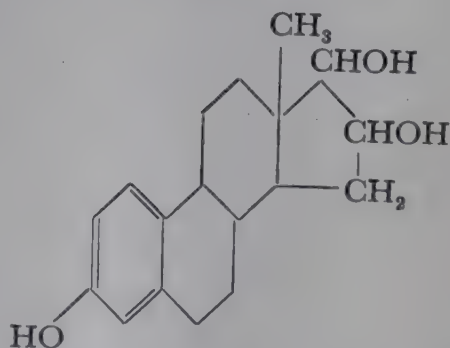
The formation of bile acids in the organism doubtless depends on the cholesterol metabolism. They are degradation products of cholesterol compounds, formed by oxidation.

Sex hormones.¹ The male and female *sex hormones*, produced by the testes and ovaries, belong to the class of cholesterol derivatives. They are responsible for the development of the specific male and female sexual characteristics. The compounds are excreted by man and horses in the urine (partly in the conjugated form, probably with glucuronic acid, and sulphuric acid (oestrone sulphate)), which is therefore a valuable source for the preparation of these substances.

A. FOLLICULAR HORMONES. As regards the female sex hormones, different substances have been isolated. The investigation of their constitution, which has been carried out particularly by Butenandt, Doisy, Girard, Marrian, and others, has shown them to be closely related chemically. They are ketones, or compounds closely related to ketones, which have the carbon skeleton of cholesterol. The following belong to the most important compounds of this group:

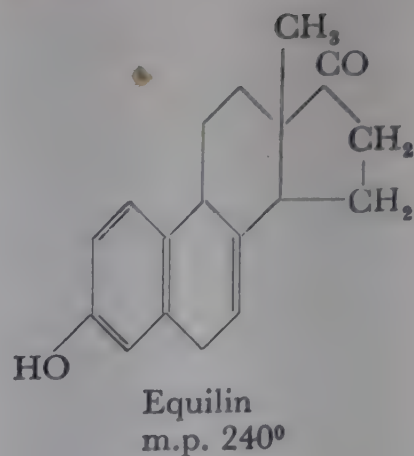
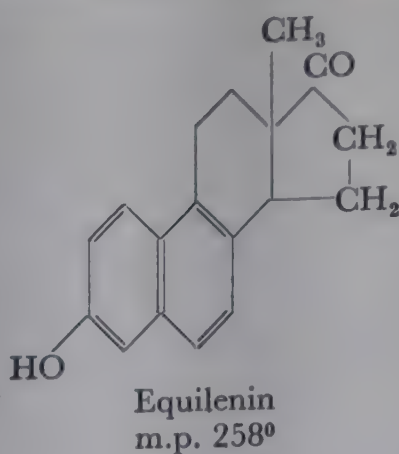
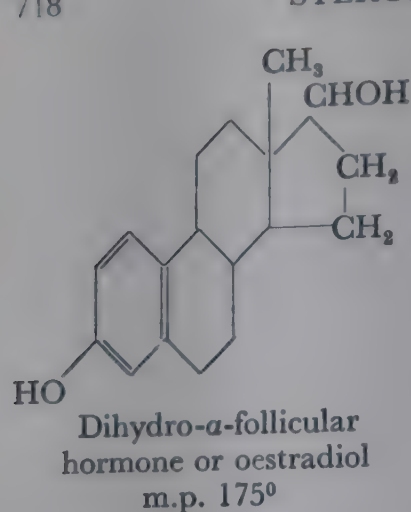


α -Follicular hormone or oestrone
m.p. 255°, $[\alpha]_D = +156-158^\circ$



α -Follicular hormone hydrate or oestriol
m.p. 280°, $[\alpha]_D = +30^\circ$

¹ Recent works on hormones: FRITZ LAQUEUR, *Hormone und innere Sekretion*, 2nd. ed. Dresden and Leipzig, (1934). — MAX REISS, *Die Hormonforschung und ihre Methoden*, Berlin and Vienna, (1934). — PAUL TRENDLENBURG, *Die Hormone. Ihre Physiologie und Pharmakologie*, Berlin, (1934). — B. HARROW and C. P. SHERWIN, *The Chemistry of the Hormones*, London, (1934). — H. M. EVANS and others, *The growth and gonad-stimulating hormones of the anterior hypophysis*, London, (1934). — L. F. FIESER and M. FIESER, *Natural products related to phenanthrene*, 3rd ed., New York, (1949). — REMY COLLIN, *Les hormones*, Paris, (1938). — CH. BOMSKOV, *Methodik der Hormonforschung*, Leipzig, (1939). — HELLMUT BREDERECK, ROBERT MITTAG, *Vitamine und Hormone*, 3 vols., (1938-39). — S. HARRIS and KENNETH V. THIMANN, *Vitamins and Hormones*, Vol. I-VI, New York, (1945-48). — GREGORY PINGUS and KENNETH V. THIMANN, *The Hormones*, Vol. I and II, New York, (1948-49).

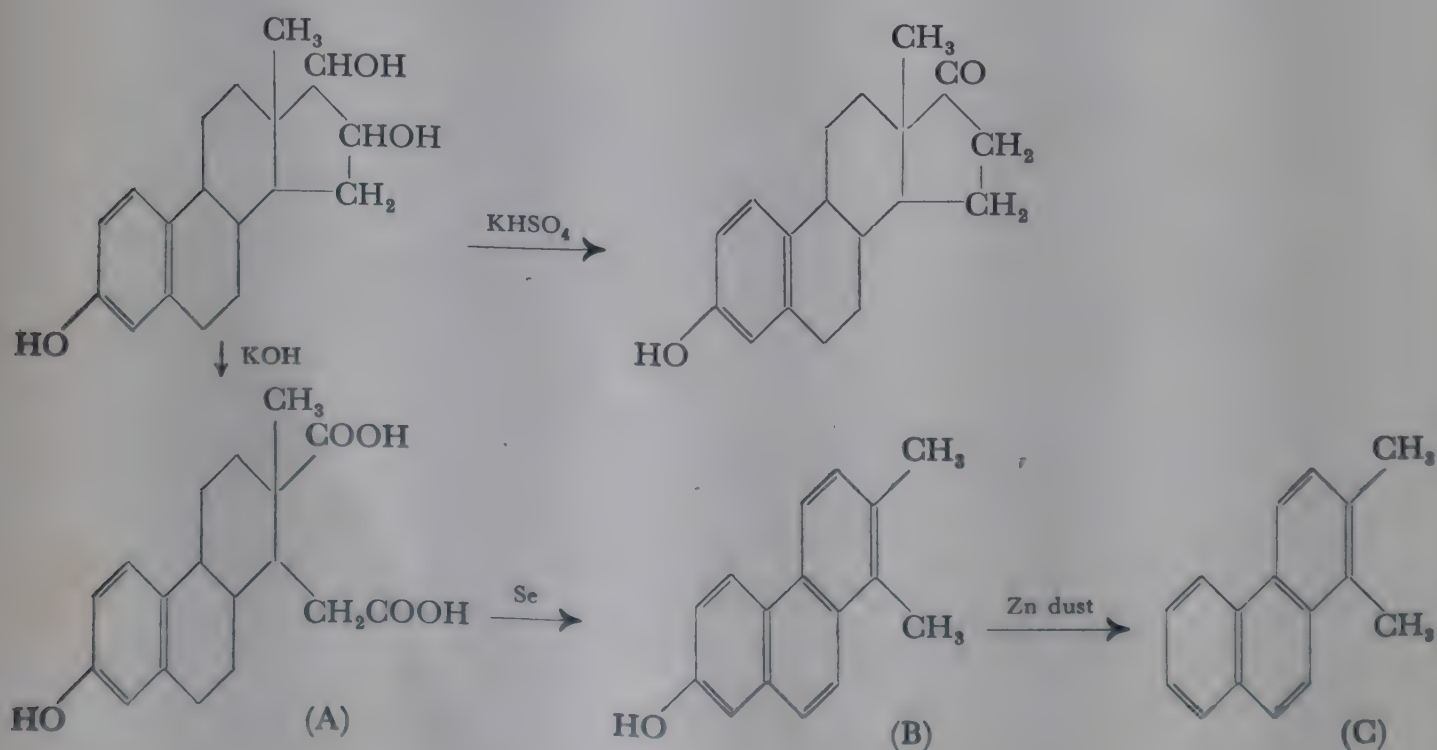


The last three follicular hormones have been isolated from the urine of mares. Oestrone (α -follicular hormone) exceeds in quantity all the other compounds of this class occurring in urine. The paradoxical fact has been discovered (B. Zondek) that the urine of *stallions* contains the largest proportion of follicular hormones. An explanation of this has not yet been offered. The following data have been found for the quantity of follicular hormones:

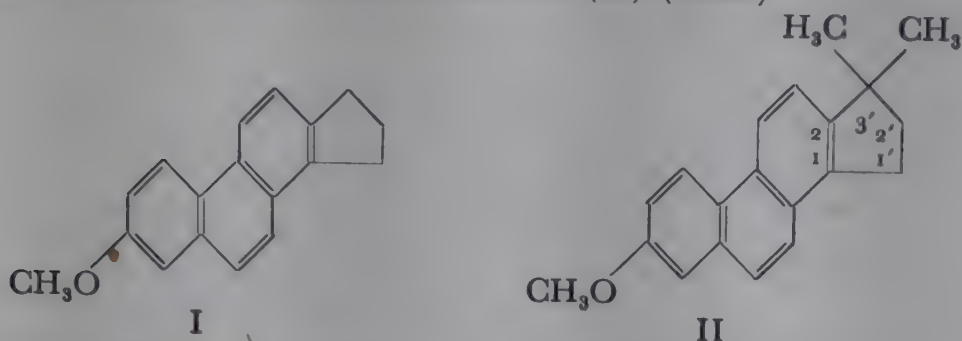
in the urine of pregnant women about	20,000–40,000	mouse units per litre
„ „ „ „ pregnant mares	„ 100,000–200,000	„ „ „ „
„ „ „ „ stallions	„ 200,000–350,000	„ „ „ „

Also from the *testes* of stallions, oestradiol and oestrone have been isolated. Of the five follicular hormones mentioned above, oestradiol has been found to be the most active. It has been isolated by Doisy from ovarian extract. β -Oestradiol, which differs from oestradiol (α -oestradiol) in the configuration at C-atom 17, and which, for example, can be obtained from oestrone by reduction, is less active.

The constitutional formulæ of the follicular hormones given above have been supported by degradation reactions carried out with the compounds. By distillation with potassium bisulphate oestriol loses water and is converted into oestrone. If oestriol is fused with caustic potash the *cyclopentane* ring opens. The reaction product (A) can be dehydrogenated by means of selenium to a 1:2-dimethylphenanthrol (B), which is converted by distillation with zinc dust into 1:2-dimethylphenanthrene (C):

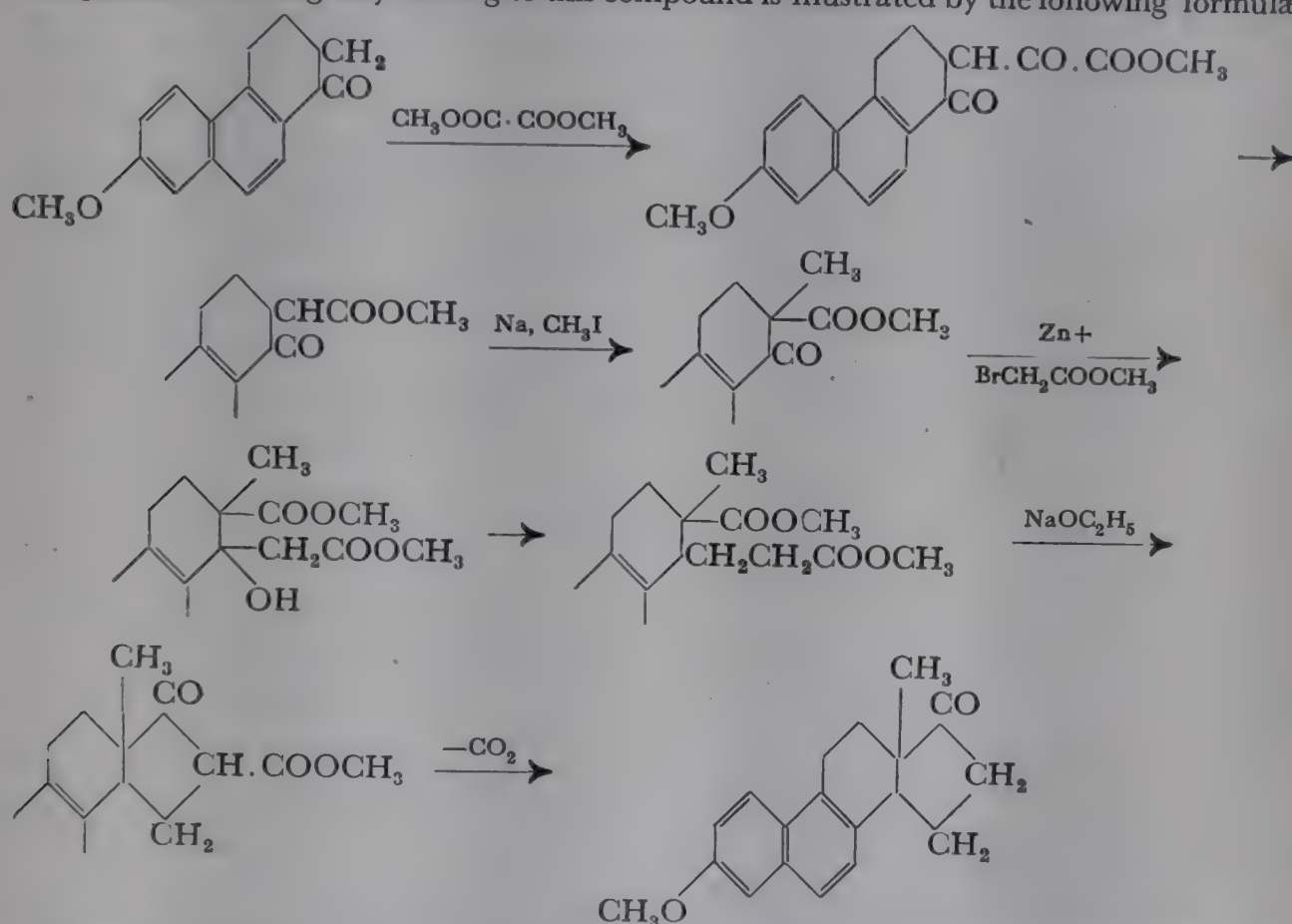


The dehydrogenation of methylated deoxooestrone and of methylated deoxo-equilenin by means of selenium to give 7-methoxy-1:2-cyclopentenophenanthrene (I), as well as the degradation of oestrone, equilin, and equilenin to 7-methoxy-3':3'-dimethyl-1:2-cyclopentenophenanthrene (II) (Cook)



are in agreement with the above constitutional formulæ for these hormones.

W. E. Bachmann succeeded in effecting the first total synthesis of a follicular hormone, viz. *equilenin*. The long way leading to this compound is illustrated by the following formulæ:

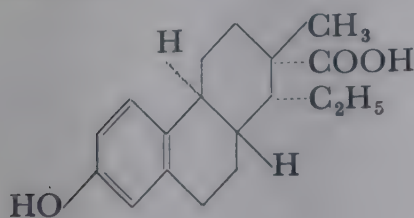


More recently, oestrone also has been synthesized in an essentially similar way by Anner and Miescher. These authors started from the keto-acid K. Theoretically, four racemic isomers of this compound are possible; one of these forms, with the m.p. 133–135°, was used as the starting material for the oestrone synthesis, which passed through analogous intermediate products as in the Bachmann synthesis of equilenin.



The work of Dodds, R. Robinson, and others, has led to the discovery of various

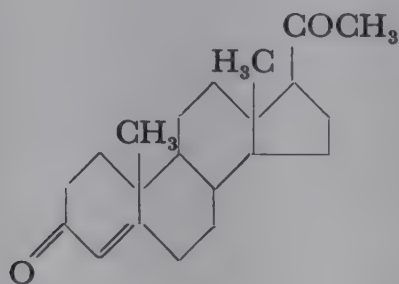
synthetic compounds of simple structure possessing fully the physiological effects of the follicular hormones. *p,p'*-Dihydroxy-diethylstilbene (*trans*-configuration), shown above, even exceeds oestradiol in oestrogenic activity and has been introduced into therapeutics under the name "*stilboestrol*". φ -Stilboestrol (m.p. 151°), stereoisomeric (*cis-trans*-isomeric) with stilboestrol (m.p. 171°), is less active. Also the diphenylethane derivative produced by reduction of the double bond in stilboestrol has oestrogenic activity when in the *meso*-form.



Another oestrogenically very active substance is the so-called doisyonic acid, a 7-hydroxy-2-methyl-1-ethyl-1:2:3:4:9:10:11:12-octahydrophenanthrene-2-carboxylic acid. Several of the sixteen theoretically possible isomers have been synthesized by K. Miescher and co-workers. The most active form corresponds to the configuration shown.

B. HORMONES FROM THE CORPUS LUTEUM. In the yellow bodies or corpora lutea of the ovaries, are contained hormones which like the follicular hormones affect the uterus in a definite manner. These compounds are called *progesterones*. They have been investigated chiefly by Slotta, Butenandt, Allen and Wintersteiner, Hartmann and Wettstein, and others.

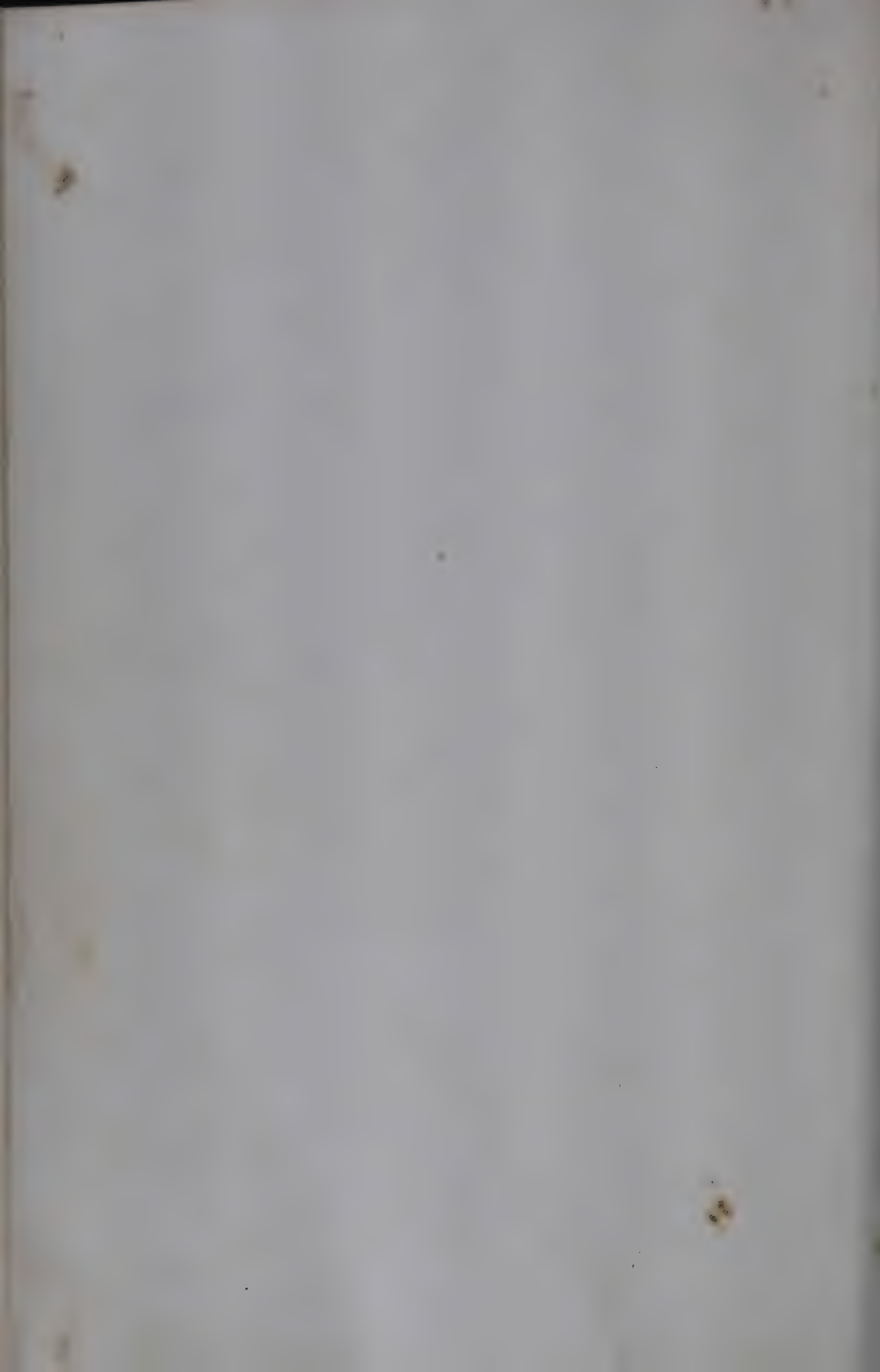
In addition to an inactive hydroxy-ketone, $C_{21}H_{34}O_2$, melting at 194°, two active ketones, $C_{21}H_{30}O_2$, of melting point 121° and 128° respectively, have been isolated. They are polymorphic modifications, and can easily be converted one into the other. The ketone of melting point 128° is known as α -*progesterone*. It has the constitutional formula given below, and is thus a derivative of cholesterol, the hydroxyl group of which has been oxidized to a keto-group, and whose side chain has been broken down to an acetyl group:

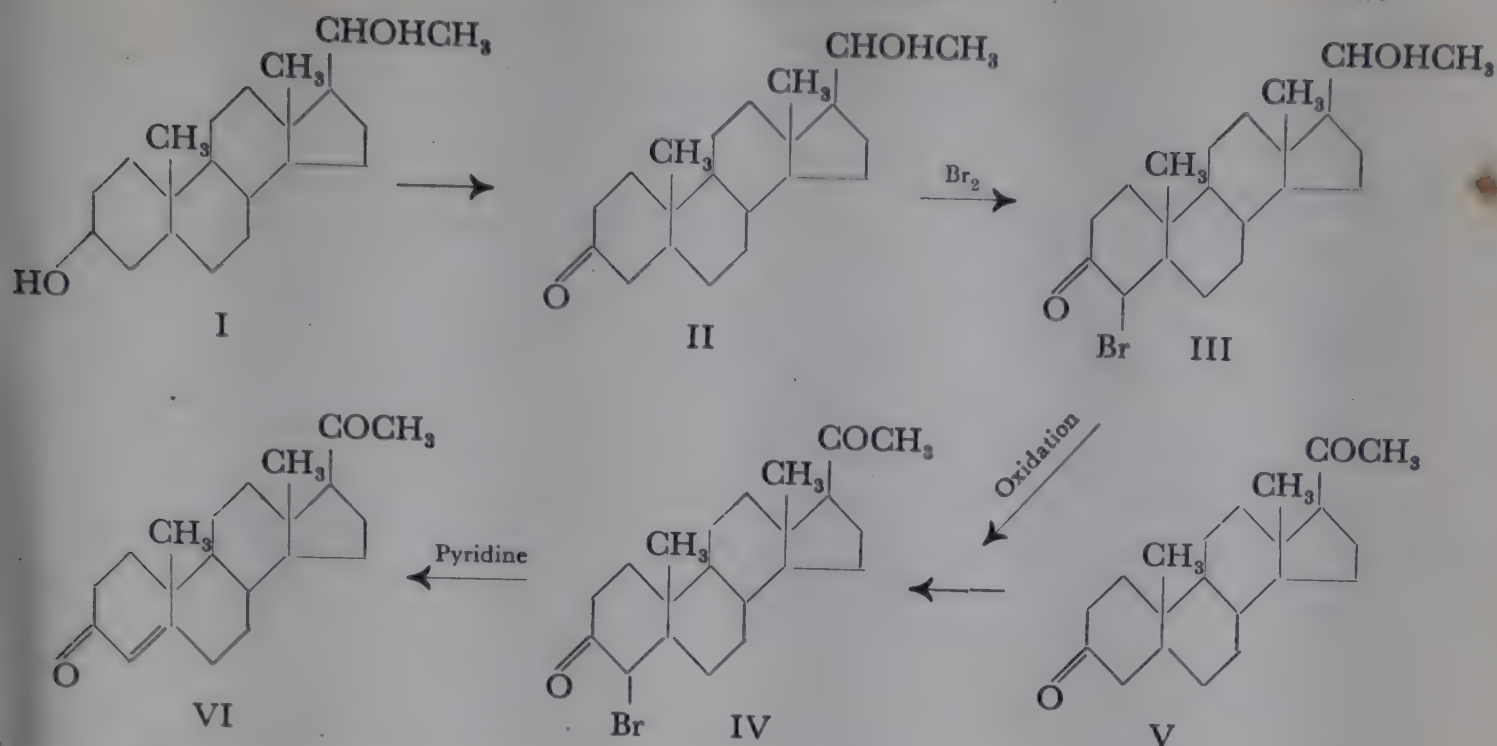


Accordingly, progesterone has also been prepared artificially from cholesterol and cholanic acid derivatives.

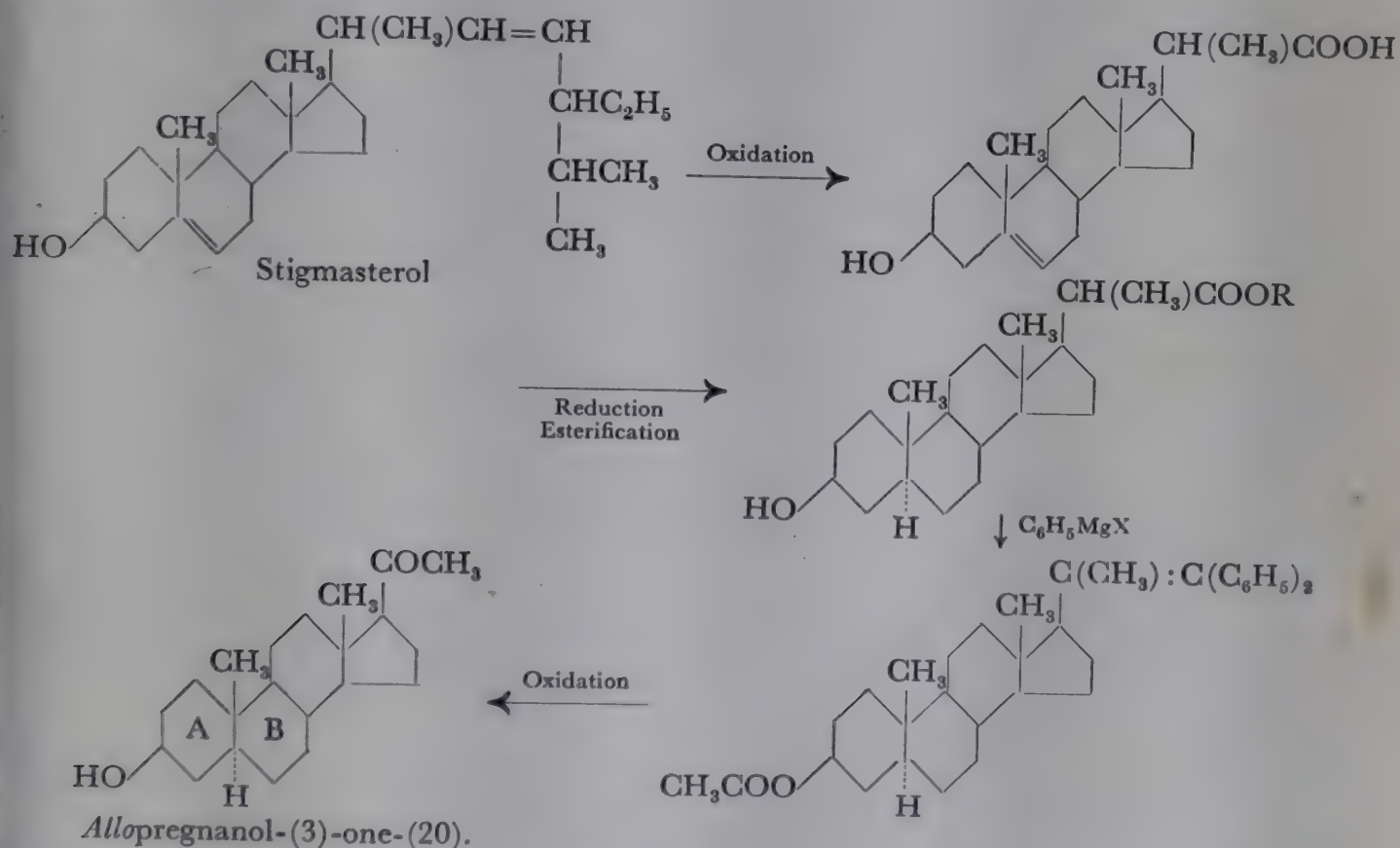
One such synthesis starts from *pregnanediol*. This dihydric alcohol, a stable, physiologically inactive substance, is found (together with the stereoisomeric *allo*-pregnanediol) in pregnancy urine, and differs from dihydrocholesterol in possessing a different side chain. Instead of the grouping $-\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)_2$ which occurs in dihydrocholesterol, pregnanediol has the side chain $-\text{CHOHCH}_3$ (formula I). The parent hydrocarbon *pregnane* has also been obtained by degradation of cholanic acid.

Pregnanediol (I) is converted by oxidation into pregnanol-(20)-one-(3) (formula II). The latter is brominated in glacial acetic acid solution and the bromo-compound (III) is converted into the bromo-diketone (IV) by oxidation with chromic acid. This diketone can also be obtained by direct bromination of pregnanedione (V). Pyridine eliminates hydrogen bromide from (IV) giving α -progesterone (VI):





The physiologically inactive *hydroxy-ketone* $\text{C}_{21}\text{H}_{34}\text{O}_2$ from the corpus luteum, which R. E. Marker also found in the urine of pregnant women, can be regarded as a hydrogenation product of α -progesterone. It has the constitution of *allopregnanol*-(3)-one-(20), and has been obtained synthetically by the degradation of stigmasterol in the following way:



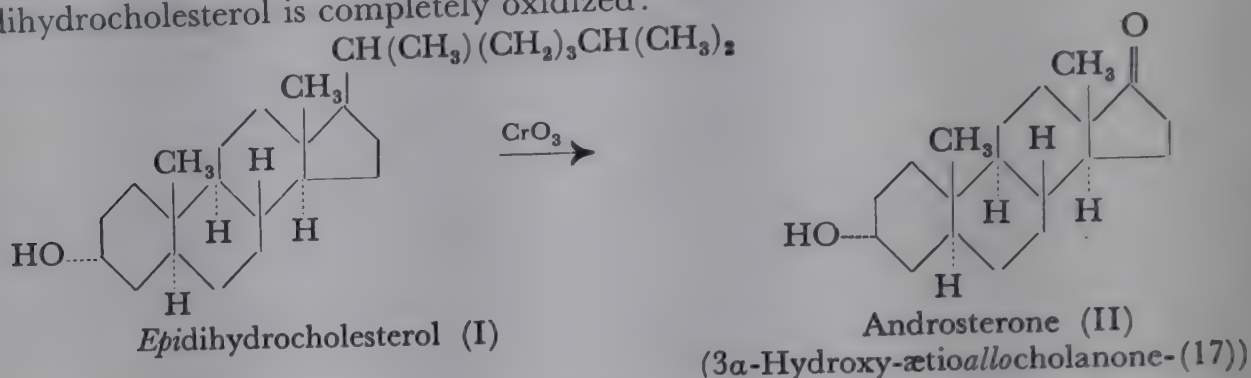
The junction of rings A and B is *trans*. The compound is derived from the dihydrocholesterol series (*allocholan*ic acid series).

C. TESTICULAR HORMONES. Butenandt isolated two crystalline compounds from the urine of males, which originate in the testes, and which can develop male sexual characteristics in castrated male animals. The one, the more active com-

pound, is *androsterone*, a ketone, $C_{19}H_{30}O_2$, melting at $182-183^\circ$, which is converted by reduction into the even more active dihydroandrosterone. The second hormone is a dehydroandrosterone, $C_{19}H_{28}O_2$, which is converted by reduction into an *isoandrosterone*.

The constitutional formula for androsterone (II), put forward by its discoverer, shows the close constitutional connection between the compound and the follicular and corpus luteum hormones and cholesterol. Androsterone is thus the derivative of a reduced cholesterol, whose aliphatic side chain has been completely removed by oxidation. In its place there appears in the *cyclopentane* ring of the cholesterol carbon skeleton a keto-group.

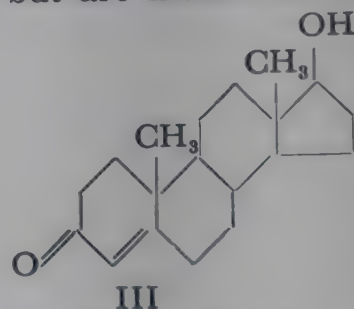
Correspondingly, Ruzicka succeeded in preparing androsterone synthetically by the oxidation of *epidihydrocholesterol* with chromic acid. The side chain of the *epidihydrocholesterol* is completely oxidized:



The conversion of *epidihydrocholesterol* into androsterone also gives an insight into the steric structure.

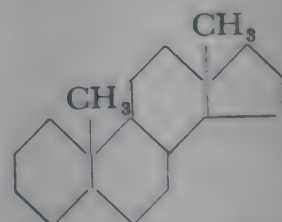
As was explained on p. 715, *epidihydrocholesterol* is probably the *cis, trans, trans, trans* isomeride. The same steric structure must also be present in androsterone. The compounds dihydrocholesterol, coprosterol, and *epicoprosterol* which are isomeric with *epidihydrocholesterol*, can be oxidized by chromic acid to ketones, which are stereoisomeric with androsterone, but are much less active physiologically.

E. Laqueur and his co workers later found a further male sex hormone in the testes, *testosterone*, which is considerably more active than androsterone. It melts at 154.5° . The formula III has been proved for this compound from its synthesis (Ruzicka, Wettstein, etc.).



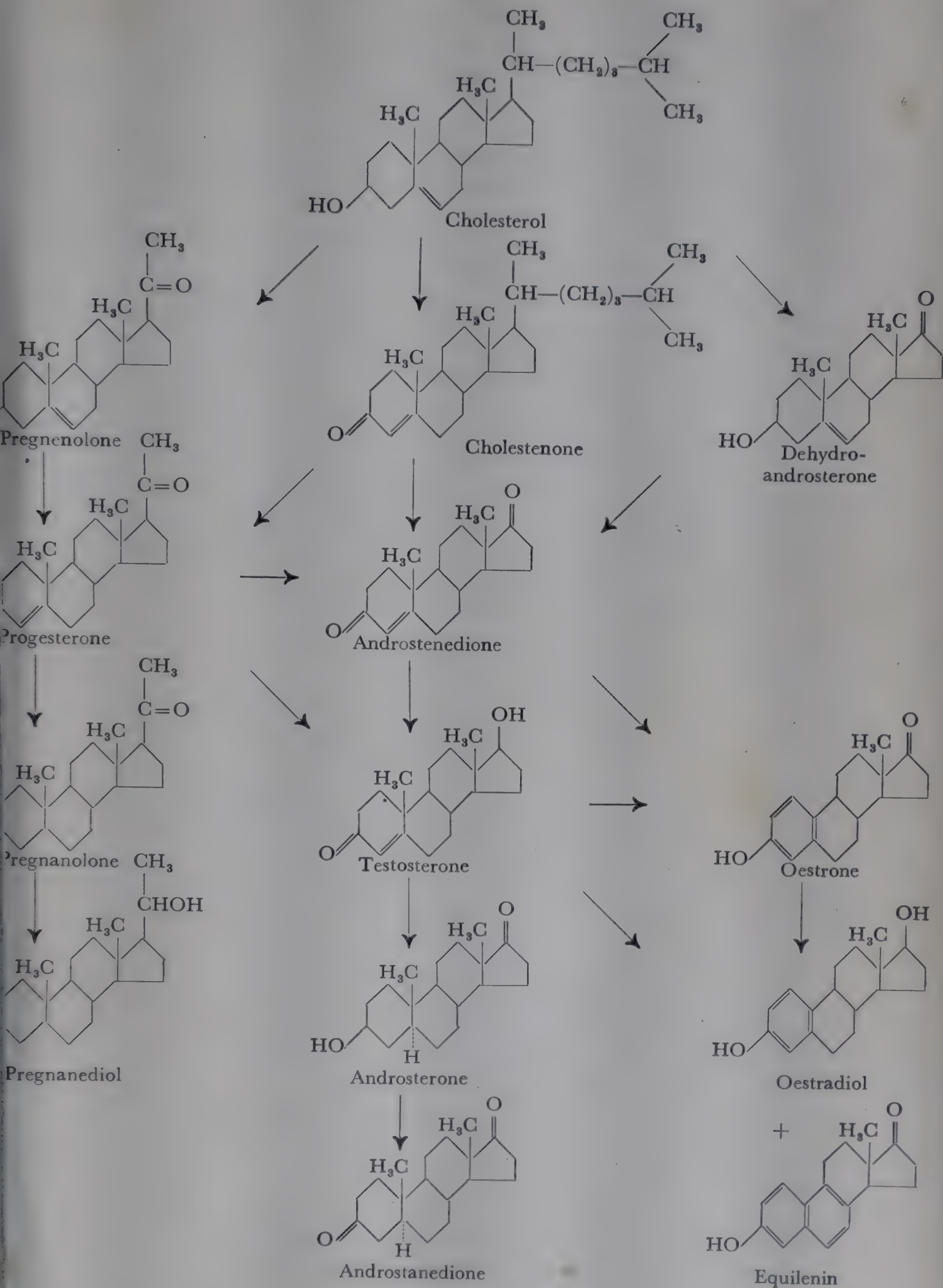
This synthesis depends on the catalytic hydrogenation of dehydroandrosterone to the unsaturated diol, partial hydrolysis in the position 3 of a di-ester of the latter, oxidation of the free hydroxyl group in position 3 to the keto-group, during which the double bond wanders into the α, β -position to the carbonyl, and finally hydrolysis of the ester group in position 17.

The parent hydrocarbon of androsterone and testosterone is called *androstan*. It has become customary to give the prefix α to substituents which, in the projection formula of this hydrocarbon, lie *behind* the plane, and β to those in *front* of the plane. Androsterone therefore may be denoted in this nomenclature as androstanol-(3 α)-one-(17).



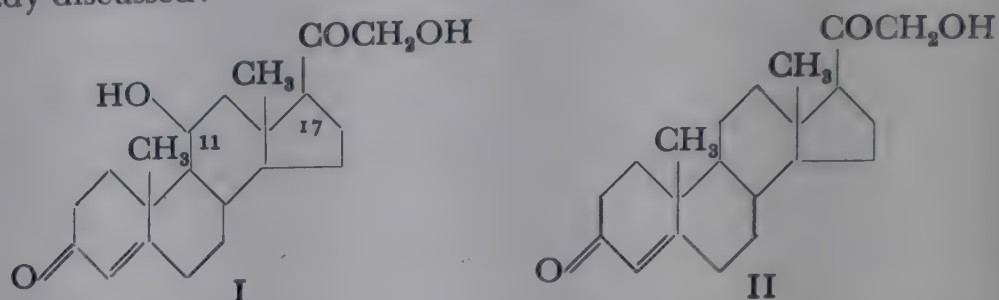
The constitutional relationships between the different sex hormones and cholesterol are given in the scheme on p. 723¹.

¹ Hypothetical, chiefly due to Butenandt and Ruzicka.

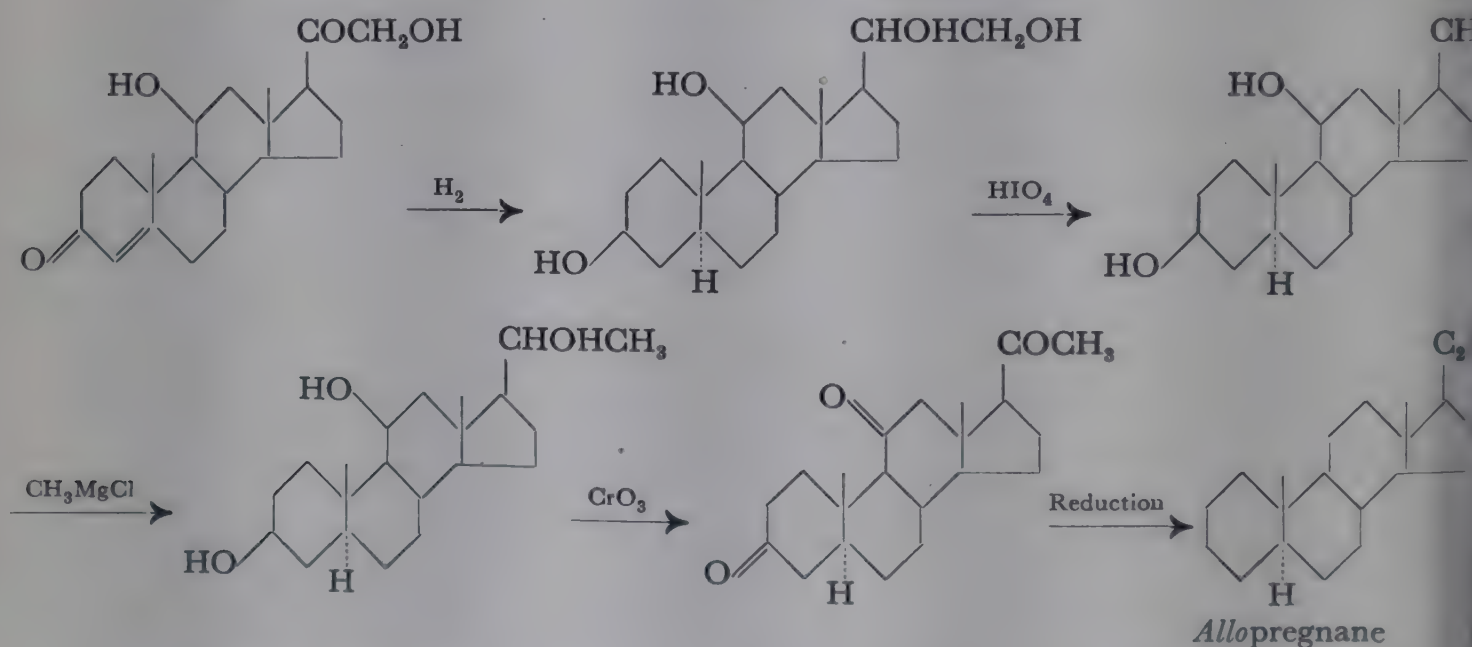


Hormones of the adrenal cortex. The hormones of the adrenal cortex, which find use in medicine for the treatment of Addison's disease, belong, like the sex hormones, to the group of sterols. Kendall and Reichstein have isolated different crystalline substances from the adrenal cortex, of which the most active are *corticosterone* (I) and *deoxycorticosterone* (II).

The constitution of corticosterone has been largely elucidated by the work of Reichstein. The formula below shows the close connection between this substance and the sterols already discussed:



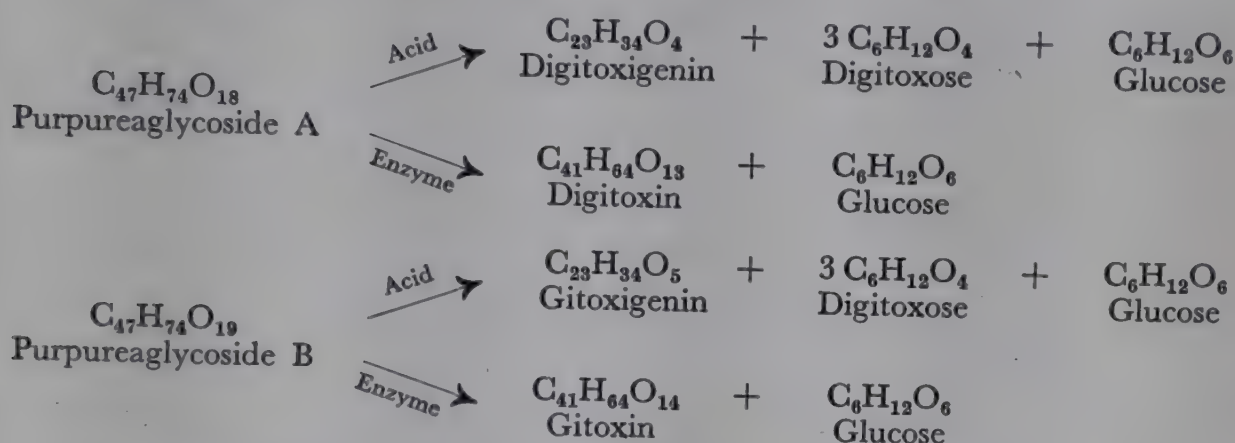
The side chain $\text{—COCH}_2\text{OH}$ in position 17 appears to be essential for the activity of the substance, while the hydroxyl group in position 11 is less important. Deoxycorticosterone II, which has been synthetically prepared and only differs from corticosterone by the absence of the hydroxyl at C-11, is even more active than corticosterone itself. That corticosterone belongs to the group of sterols was proved by its degradation to *allopregnane*:



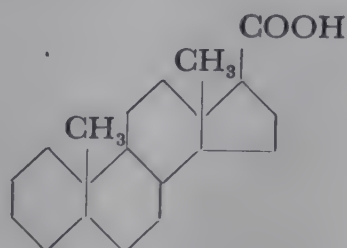
sterols, but it is only within recent years that the work largely of Jacobs, Tschesche, Stoll, and others, has shown with certainty their connection with the group of sterols, bile acids, etc.

The *digitalis glycosides* are found in the leaves of varieties of *digitalis* (*Digitalis purpurea*, *Digitalis lanata*). Related compounds, however, have also been found in other plants, e.g. strophanthin in species of *strophanthus*. They have a powerful action on the heart, and have considerable practical use for the regulation of heart activity.

The crystalline glycosides *digitoxin* and *gitoxin* were already isolated from *Digitalis purpurea* some time ago. The further work of A. Stoll has shown, however, that these are not genuine compounds, but are products of hydrolysis, which have been produced from the glycosides originally present in the plant by partial hydrolysis during the process of isolation. The true glycosides from *Digitalis purpurea* are *purpureaglycoside A* and *purpureaglycoside B*, which are broken down by enzymes into digitoxin and glucose, and gitoxin and glucose, respectively. Acids bring about complete hydrolysis to the aglycones digitoxigenin and gitoxigenin, the desoxy-sugar digitoxose, $\text{CH}_3(\text{CHOH})_3\text{CH}_2\text{CHO}$, and glucose:

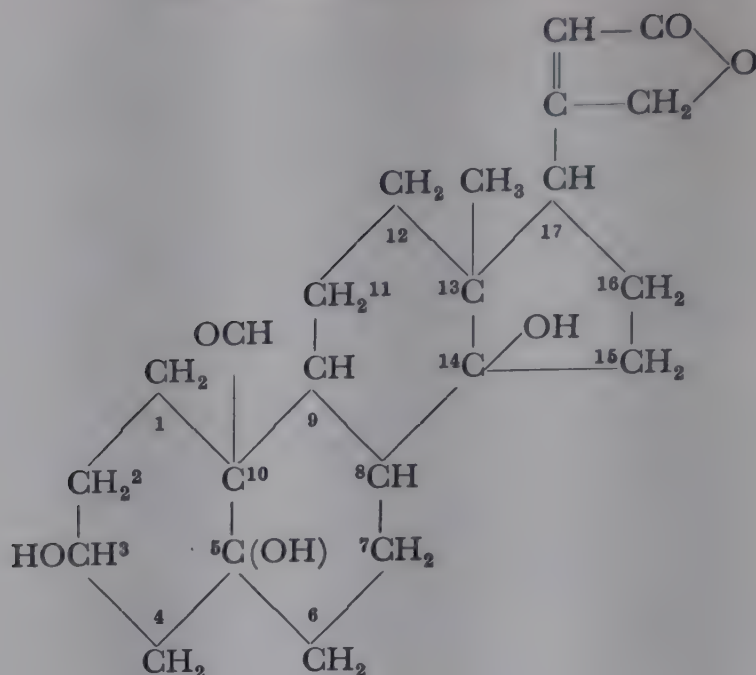


The investigation of the constitution of the aglycones from the *digitalis* glycosides and similar compounds has begun only in recent years. These "genins" are lactones, of which the carbon skeleton is that present in the sterols. Thus it is possible by selenium dehydrogenation to prepare a hydrocarbon $\text{C}_{18}\text{H}_{16}$ from the genins *strophanthidin* and *uzarigenin*. The same hydrocarbon is obtained from the sterols and bile acids. It is a methylcyclopentenophenanthrene (p. 714). All these compounds have also been converted into dimethylphenanthrene. Further, it has been possible to obtain *ætioallocholan*ic acid and *ætiochol*anic acid by degrad-



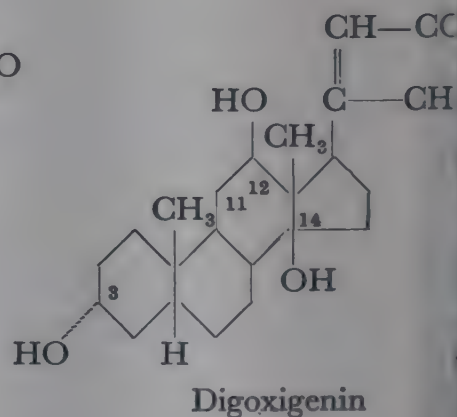
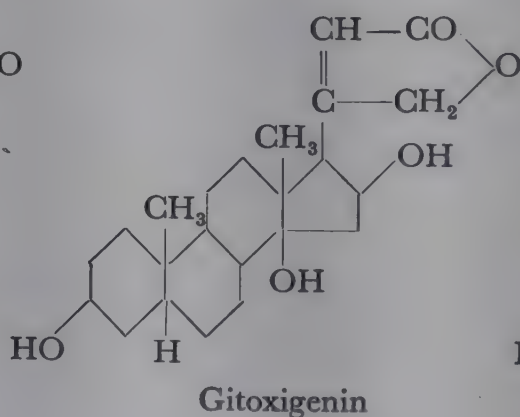
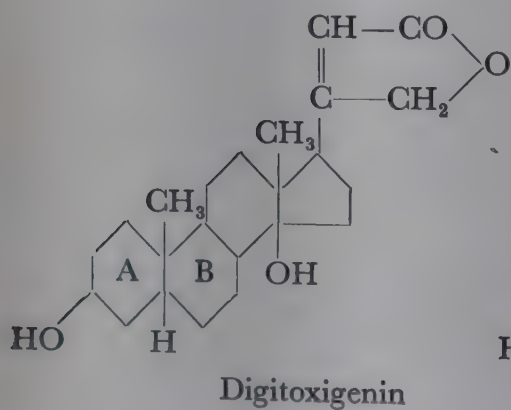
ation from *uzarigenin* and *digitoxigenin*, respectively, and *allocholan*ic acid from *scillaridin*. These acids are also formed from cholic acid derivatives.

The following formula has been proposed for *strophanthidin*:



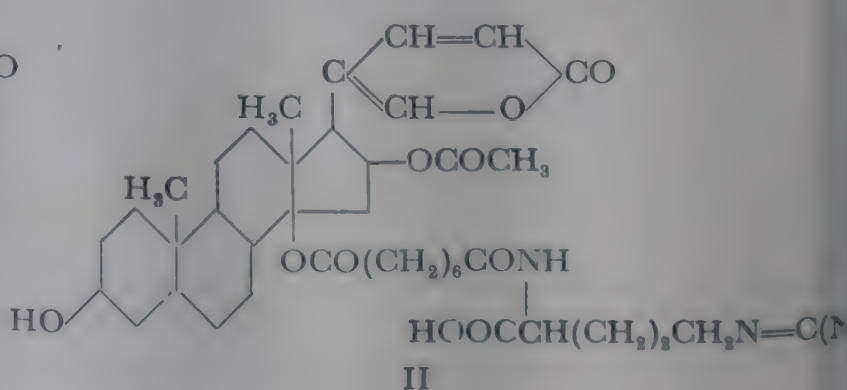
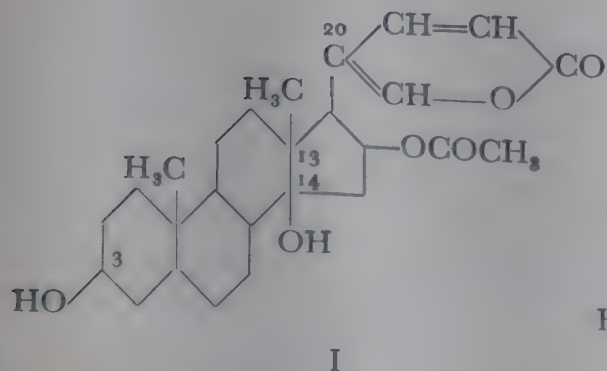
Strophanthidin occurs in nature in the form of various glycosides (e.g. K-strophanthoside, a trisaccharide with 1 molecule of the sugar cymarose and 2 molecules of glucose; cymarin, a monoglycoside with 1 molecule of cymarose, etc.).

The following constitutional formulæ have been ascribed to digitoxigenin, gitoxigenin, and digoxigenin:



In these three cardiac genins the rings A and B are fused in the *cis*-position.

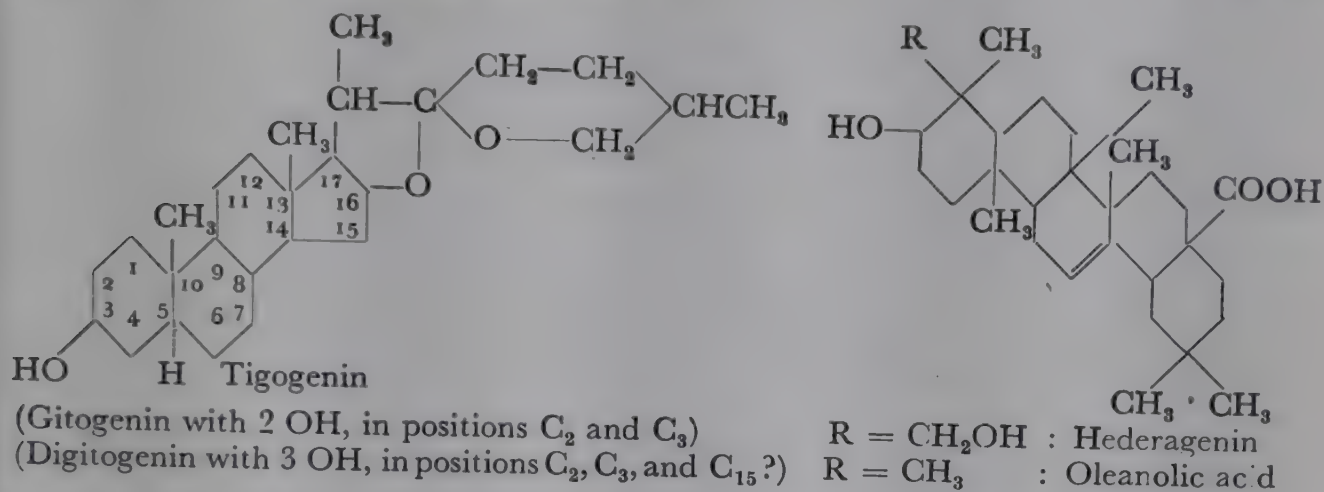
The toad poisons *bufotalin* (I) and *bufotoxin* (II) also belong to this class of compound, and, according to H. Wieland and K. Meyer, have the following formulæ:



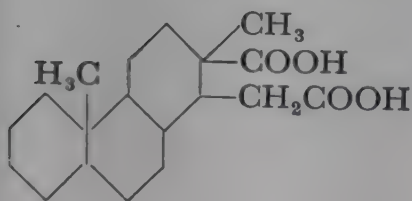
The saponins¹ are also complex substances occurring widely in plants, and which produce foams in water like soap. They are characterized by strong hæmolytic action, and are therefore powerful poisons. They combine with cholesterol to form insoluble double compounds by means of which they are rendered harmless to the organism.

The saponins are glycosides. Their aglycones belong to two different groups. The first gives methylcyclopentenophenanthrene on dehydrogenation, and is therefore related to the sterols. The second gives 1:2:7-trimethylnaphthalene (sapotalene) on dehydrogenation with selenium, a hydrocarbon which has also been obtained from various triterpene compounds.

Members of the first group are *tigogenin*, *gitogenin*, *digitogenin*, and *sarsasapogenin*. *Hederagenin* and *oleanolic acid*, for example, belong to the second group. The following formulæ have been put forward for these:



The degradation of tigogenin to ætioallobilianic acid by R. Tschesche, and to dihydroandrosterone by R. E. Marker, has proved that the steroid sapogenins contain the same carbon skeleton as the sterols. *Sarsasapogenin* appears to be stereoisomeric with tigogenin, and differs from the latter by a change of configuration at the C-atom 5 and also in the configuration of the side chain. (i.e. at C-atom 22).



Vitamins²

By vitamins are understood substances which are absolutely necessary in addition to fats, proteins, carbohydrates, and mineral salts for the normal development of the animal organism, but in very small amounts. Lack of vitamins leads

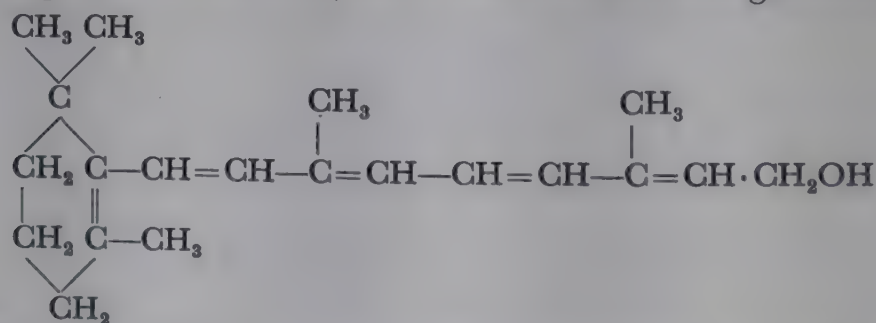
¹ See ABDERHALDEN, *Biochem. Handlexikon*, VII, 145 (R. Kobert). — ABDERHALDEN, *Handbuch der organischen Arbeitsmethoden*, Abt. I. Chemische Methoden, Teil 10. Pflanzenverb. 1, p. 555. — L. KOFLER, *Die Saponine*, Vienna, (1927).

² HENRY CLAPP SHERMAN and SYBIL LAURA SMITH, *The vitamins*, 2nd ed., New York, (1931). — H. VALENTINE KNAGGS, *The story of vitamins*, London, (1929). — TONI GORDONOFF, *Les vitamines et le problème des vitamines*, Paris, (1931). — A. R. AYKROYD, *Vitamins and other dietary essentials*, London, (1933). — CH. BOMSKOV, *Methodik der Vitaminforschung*, Leipzig, (1935). — N. N. IVANOV and others, *The Problem of the Vitamins*, Leningrad, (1934-1937). — HANS VOGEL, *Chemie und Technik der Vitamine*, Stuttgart, (1940). — G. LUNDE, *Vitamine in frischen und konservierten Nahrungsmitteln*, Berlin, (1940). — H. R. ROSENBERG, *Chemistry and Physiology of the Vitamins*, New York, (1942). — W. H. EDDY, *What are the Vitamins?* New York, (1945). — R. S. HARRIS and K. V. THIMANN, *Vitamins and Hormones*, Vols. I-VI, New York, (1943-48). See also p. 717.

to deficiency symptoms, the so-called *avitaminoses*. The above definition of vitamins, however, requires some qualification. The number of substances without which the animal body cannot develop normally is very great; amongst them are substances which are necessary in small quantities, but which, however, are not called vitamins, e.g. tryptophan or iodine. The name "vitamin" is reserved for certain organic substances, indispensable to the animal body, which have a relatively complex structure, and are comparatively unstable. The animal organism usually lacks the capacity of synthesizing them from simple substances. They are either taken up with vegetable foods, or produced in the animal organism from relatively complex compounds of plant origin.

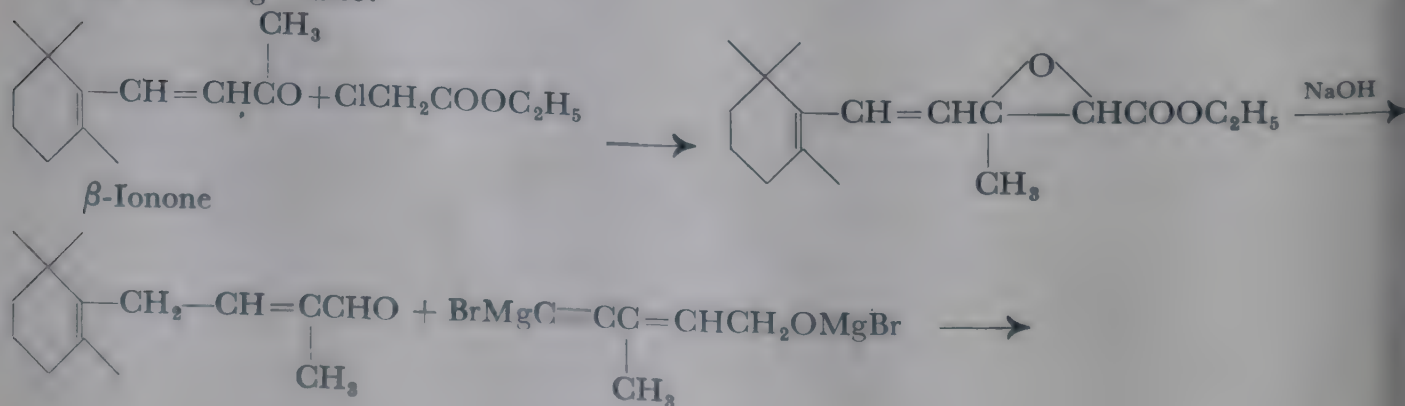
At present, about 20 naturally occurring vitamins are recognized. They are designated by letters and indices, the components of vitamin B in part by the terms B_1 to B_6 .

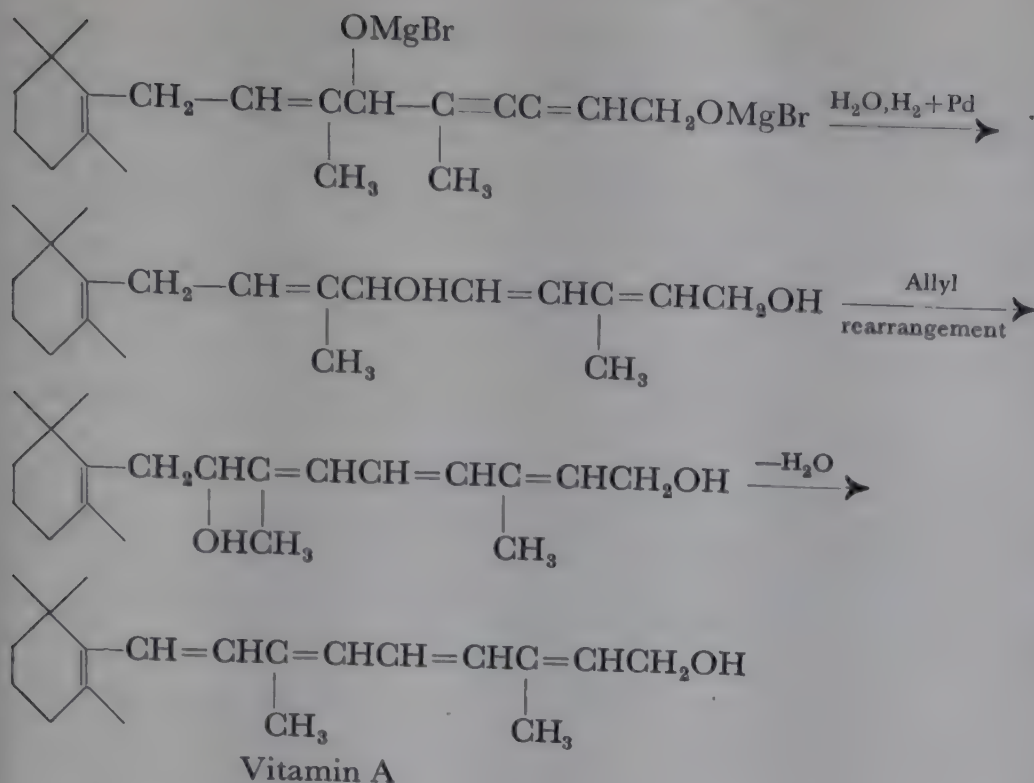
VITAMIN A is a growth-vitamin and prevents xerophthalmia (hardening of the conjunctival tissue and the cornea of the eye). As already mentioned on p. 709, carotene has this effect (H. von Euler). Carotene is not, however, identical with vitamin A, but it might be called pro-vitamin A as it is converted in the animal organism into the true vitamin A, which is stored in the liver often in very considerable quantities. Vitamin A gives an intense blue coloration with concentrated sulphuric acid and other anhydrous acids, and also with acid halides. The reaction with antimony trichloride in chloroform is used for the colorimetric estimation of the substance (Carr and Price's reaction). Vitamin A was isolated from fish liver oils, in which it occurs partly in the free state and partly as an ester, first as a yellow oil and recently also in crystalline forms. It has been characterized as a polyene by degradation reactions, which lead to the following structure (P. Karrer):



I. G. Baxter and C. D. Robeson succeeded in crystallizing vitamin A (axerophthol); they isolated the compound from fish-liver oils, in two different geometric *cis-trans*-isomeric forms. One of these compounds melts at $63-64^\circ$, and has an absorption maximum at $325 \text{ m}\mu$; the m.p. of the other form is $59-60^\circ$; it has an absorption maximum at $328 \text{ m}\mu$. Both compounds have approximately the same vitamin A activity.

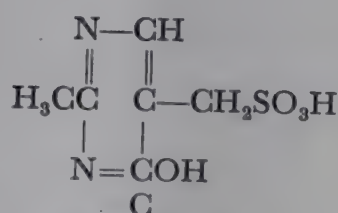
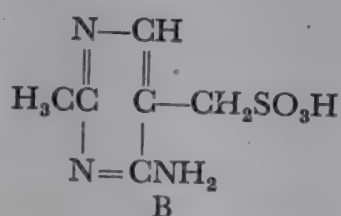
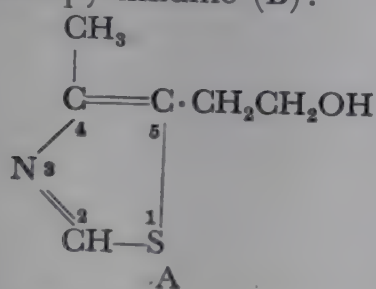
The synthesis of vitamin A has been accomplished in different ways (Arens and van Dorp; O. Isler, M. Huber, A. Ronco; N. A. Milas). One of these syntheses probably takes the following course:





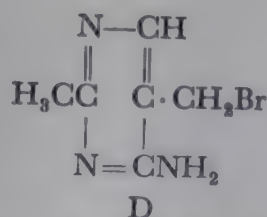
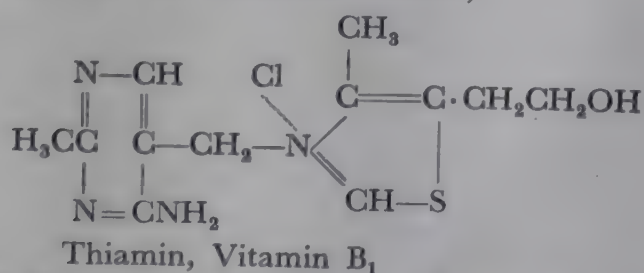
VITAMIN B₁¹ (thiamin), the vitamin which prevents beri-beri (antineuritic vitamin), is found abundantly in rice polishings, in yeast, and in the embryo of wheat, etc. C. P. Jansen and Donath were the first to isolate the crystalline substance from rice polishings, and Windaus isolated it from yeast. The molecular formula of the substance is C₁₂H₁₇ON₄SCl, HCl.

By the action of sodium sulphite on vitamin B₁, R. R. Williams succeeded in breaking down the substance into two fragments. The one is 4-methyl-5-hydroxyethyl-thiazole (A), the other is a sulphonic acid of 2:5-dimethyl-4-aminopyrimidine (B):



The constitution of the first fission product (A) is known by synthesis. The sulphonic acid (B) is partially hydrolysed by liquid ammonia to 2:5-dimethyl-4-aminopyrimidine. It can be converted into the hydroxysulphonic acid (C), of which the constitution is also known with certainty by synthesis.

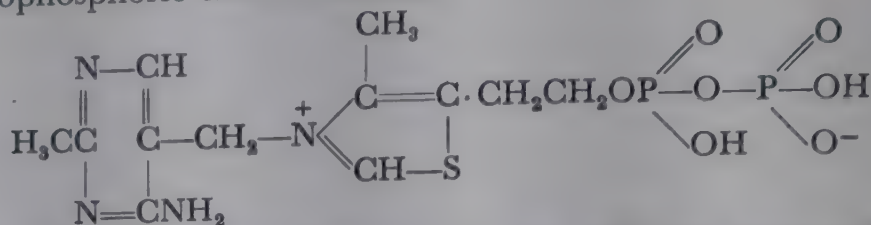
Vitamin B₁ (aneurin) has thus the peculiar structure of a quaternary thiazolonium salt (R. R. Williams, Grewe):



¹ R. R. WILLIAMS and T. D. SPIES, *Vitamin B₁ (Thiamin) and its use in Medicine*, New York, (1938).

Similar compounds were previously unknown. The formula has been finally confirmed by a synthesis of vitamin B₁. The bromo-compound (D) readily combines with methyl-hydroxyethyl-thiazole (A) to give the quaternary salt, which was found to be identical with thiamin.

The pyrophosphoric ester of thiamin.

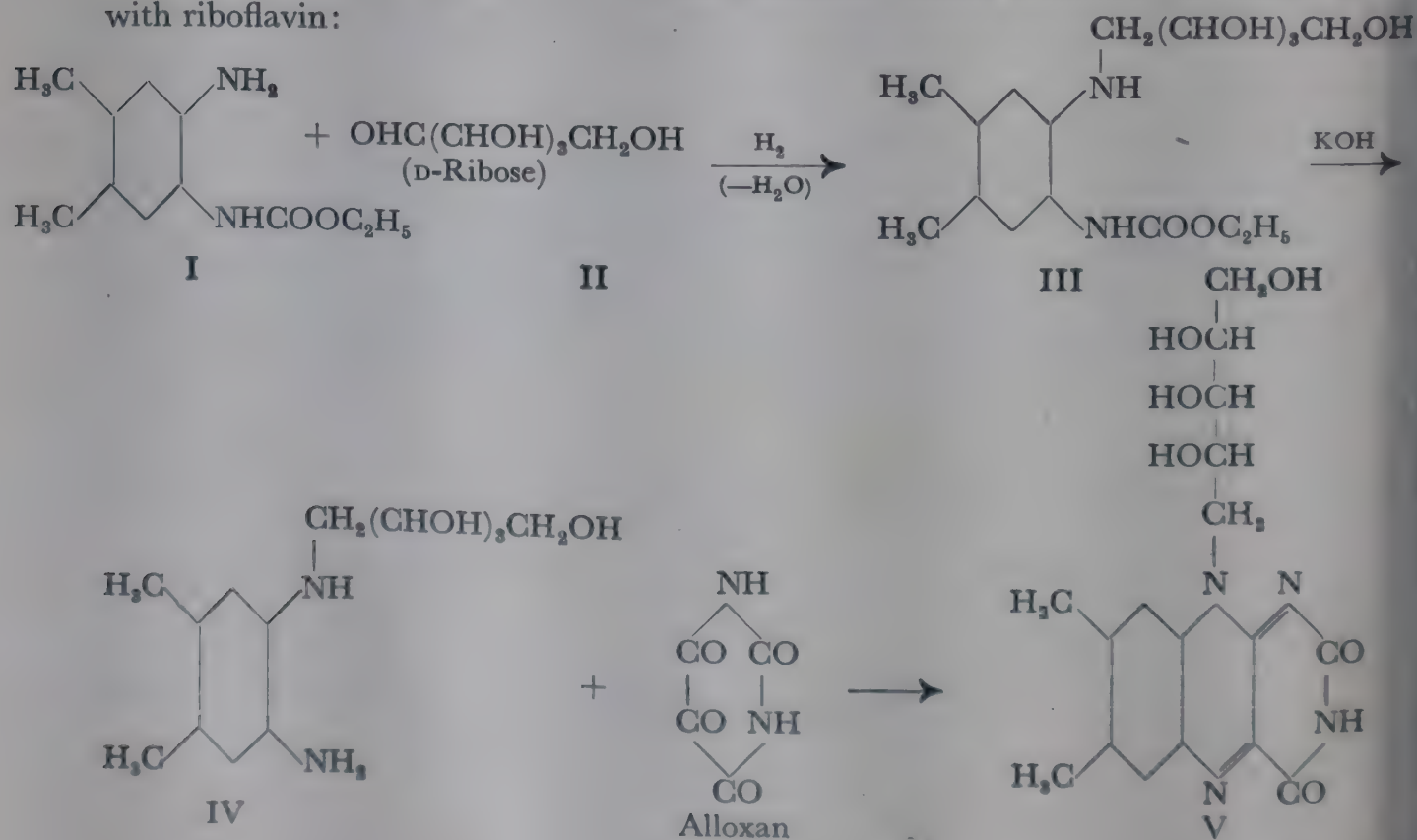


is, according to Lohmann, *coccarboxylase*, i.e. the effective group of the enzyme carboxylase which takes part in alcoholic fermentation (see p. 91). The effect of thiamin as a vitamin, its absolute necessity for the organism, depends upon the fact that it is likewise necessary for the degradation of carbohydrates. The anti-neuritic activity of coccarboxylase is about twice as great as that of thiamin itself.

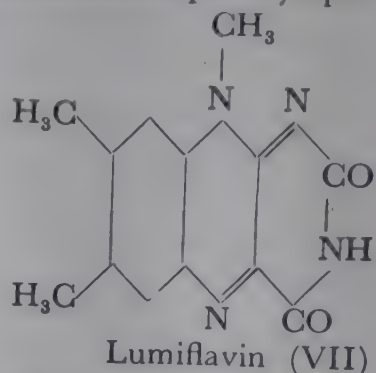
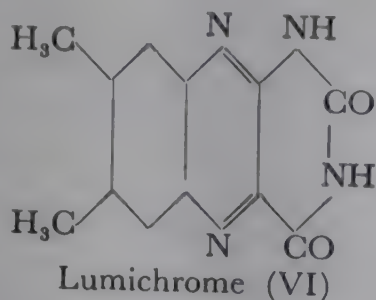
VITAMIN B₂. By this term is understood at present a water-soluble growth-factor which occurs widely in plants and in animal organs, and which is characterized by its yellow colour, a strong yellow-green fluorescence, and sensitivity to light. The chemical name of the substance is *riboflavin* or *lactoflavin*. The group of related substances is called the flavins or *lyochromes*.

Riboflavin was discovered by Warburg and Christian as a component of the so-called "*yellow oxidation ferment*", and was first obtained in the crystalline state by Kuhn. Its nature as a vitamin was recognized by György and R. Kuhn. The first total synthesis of this vitamin (Karrer) which elucidated at one and the same time its constitution and its configuration, was carried out as follows:

2-Carbethoxyamino-4:5-dimethylphenyl-ribamine (III) was prepared by hydrogenation of an equimolecular mixture of 1-amino-2-carbethoxyamino-4:5-dimethylbenzene (I) and D-ribose (II). When (III) is hydrolysed with alkali, and the 2-amino-4:5-dimethylphenyl-ribamine (IV) formed is heated with alloxan in acid solution, the flavin dye (V) was produced, which proved to be identical with riboflavin:

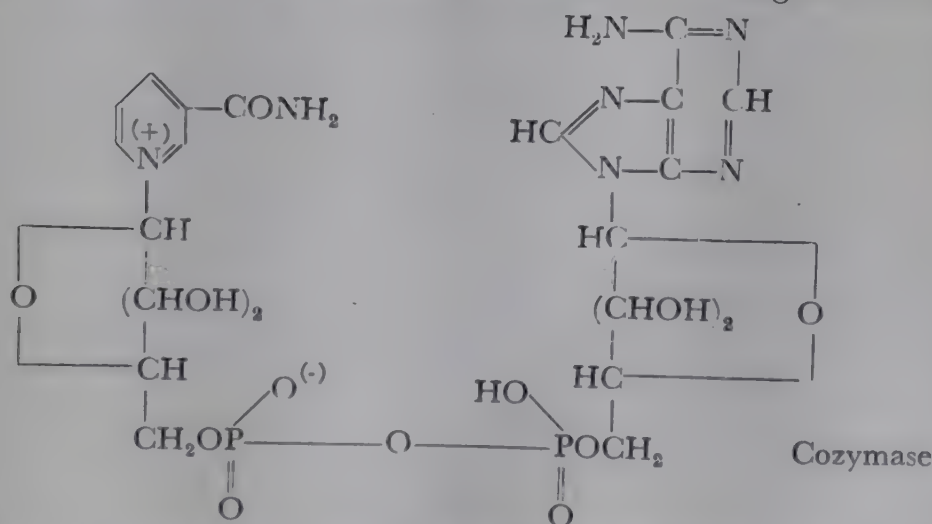


One of the most striking properties of vitamin B₂ is its great sensitivity to light. If it is irradiated in neutral solution, the ribose residue is completely split off, and 6:7-dimethyl-alloxazine or lumichrome (VI) is produced. In alkaline solution, irradiation produces partly lumichrome but to a greater extent lumiflavin, 6:7-9-trimethylisalloxazine (VII):



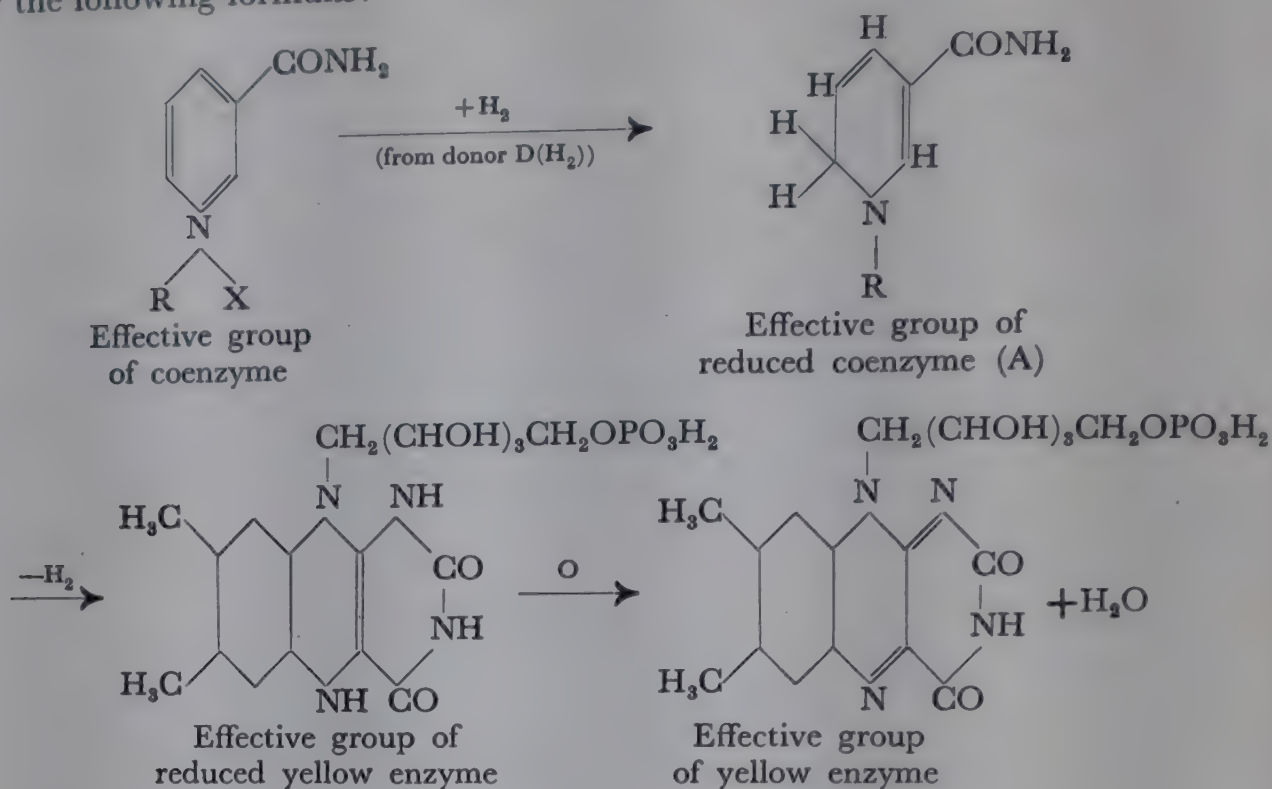
The "yellow oxidation ferment" of Warburg, which brings about dehydrogenations, is composed of a protein and a flavin phosphate. The former plays the part of a "carrier" in the enzyme, whilst the flavin phosphate is the prosthetic, active group, which, however, can act as an enzyme only in combination with the "carrier substance". Theorell has succeeded in breaking down the enzyme into its two components and recombining them.

In order that the yellow enzyme should be able to effect dehydrogenations, a *coenzyme* and a corresponding *carrier substance* (a specific protein = "intermediate ferment") are necessary. The coenzymes involved in the hydrogen transfer which are best investigated up to the present are the so-called "*hydrogen-carrying co-ferment*" of Warburg (also known as codehydrase II, or triphosphopyridine nucleotide), and *cozymase* (codehydrase I, diphosphopyridine nucleotide) of H. van Euler. Both consist of 1 molecule of nicotinamide, 1 molecule of adenine, 2 molecules of pentose, and phosphoric acid. Of the latter, triphosphopyridine nucleotide contains three, and cozymase two molecules. The hydrogen-transferring group of these two coenzymes is *nicotinamide*, which occurs as a quaternary compound. The reversible hydrogenation depends on this special state of combination. In the formulæ below representing the effective group of the coenzyme, R stands for the phosphorylated ribose-residue. The complete cozymase molecule may be represented by the following structure, according to H. v. Euler:



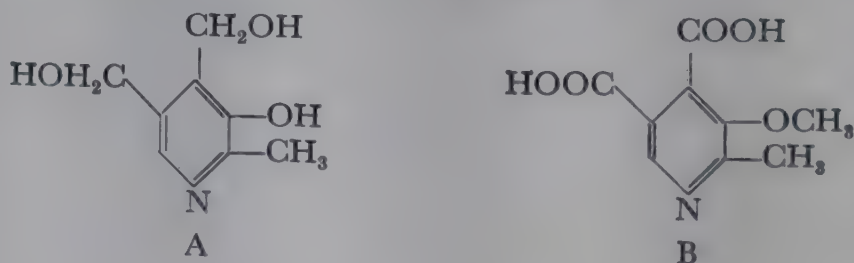
The primary reduction product which is formed by taking up the hydrogen from the donor D(H₂) is an *o*-dihydro-compound of the amide of nicotinic acid (A), which in turn gives up the hydrogen to the yellow enzyme. The hydrogenation product of the yellow enzyme is finally oxidized by atmospheric oxygen (or by other enzymes, such as diaphorase and cytochrome).

The reactions which take place at the effective groups of the two enzymes in the dehydrogenation of the donor $D(H_2)$, may be represented schematically by the following formulæ:

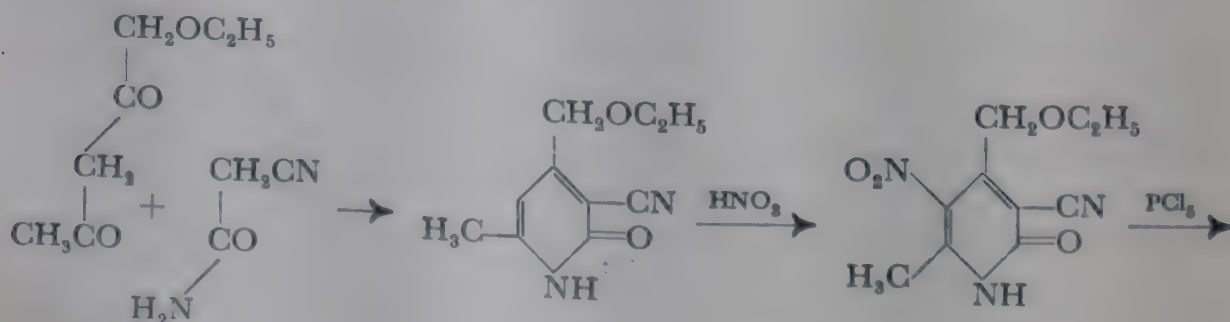


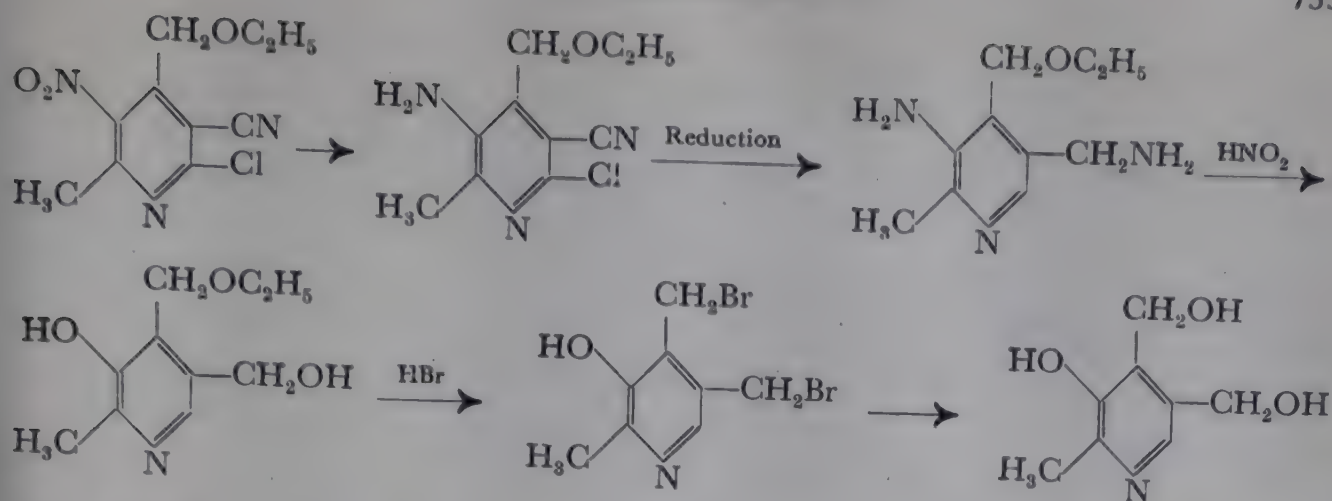
(The effective group of other "yellow enzymes" also contains adenylyl phosphate besides riboflavin phosphate, which are chemically combined).

VITAMIN B_6 , a factor necessary to cure a dermatitis in rats, has been isolated simultaneously by different workers, and has been given the trivial names *adermine* and *pyridoxine*. It is a comparatively simple pyridine derivative, viz. 3-hydroxy-4:5-bis-(hydroxymethyl)-2-methylpyridine (formula A). By oxidation with barium permanganate the pyridoxine methyl ether was converted into 2-methyl-3-methoxypyridine-4:5-dicarboxylic acid (formula B).

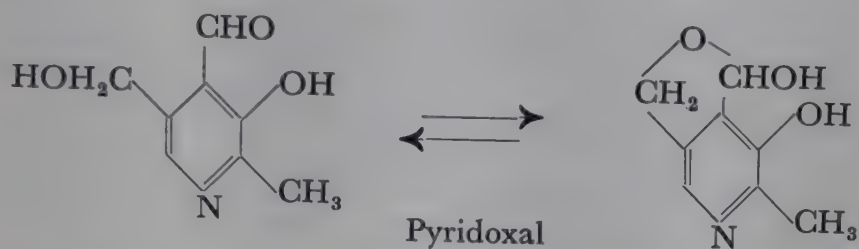


Different syntheses have been worked out for this compound. The one by St. A. Harris and K. Folkers, starts from cyanoacetamide and ethoxyacetylacetone, and proceeds as follows:





Another method for the artificial preparation of pyridoxine has been worked out by R. Kuhn, Westphal, Wendt, and Westphal. It starts with 2-methyl-3-methoxypyridine-4:5-dicarboxylic acid, which is converted, through the dinitrile, to the corresponding diamine and dihydric alcohol. The latter on demethylation with hydrobromic acid gives the dibromide identical with the penultimate reaction product of the Harris-Folkers synthesis described above.

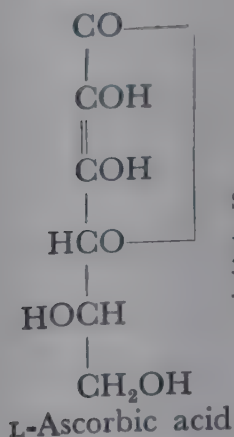


A derivative of pyridoxine, *pyridoxal*, which occurs in nature, and which can be obtained by oxidation of pyridoxine, is likewise of considerable biological importance. In the cell it is converted into a phosphoric acid ester in which probably the phenolic hydroxyl is esterified, and which acts as the coenzyme of an amino-acid decarboxylase; tyrosine, arginine, lysine, and glutamic acid are decarboxylated by this enzyme system. The coenzyme has been synthesized and obtained in a crystalline form (as the ethyl acetal).

OTHER B-VITAMINS. Among the other B-vitamins that are soluble in water, *nicotinamide* (cf. p. 731) must be mentioned. It cures pellagra and the so-called "black tongue disease" of dogs. *p*-Aminobenzoic acid, *pantothenic acid* (discovered by R. J. Williams), and biotin (p. 737) should also be referred to. There are, moreover, some other factors belonging to the vitamin-B group, whose chemical nature has not yet been elucidated. They are not adsorbed by fuller's earth and are therefore contained in the filtrate from the fuller's earth adsorbate.

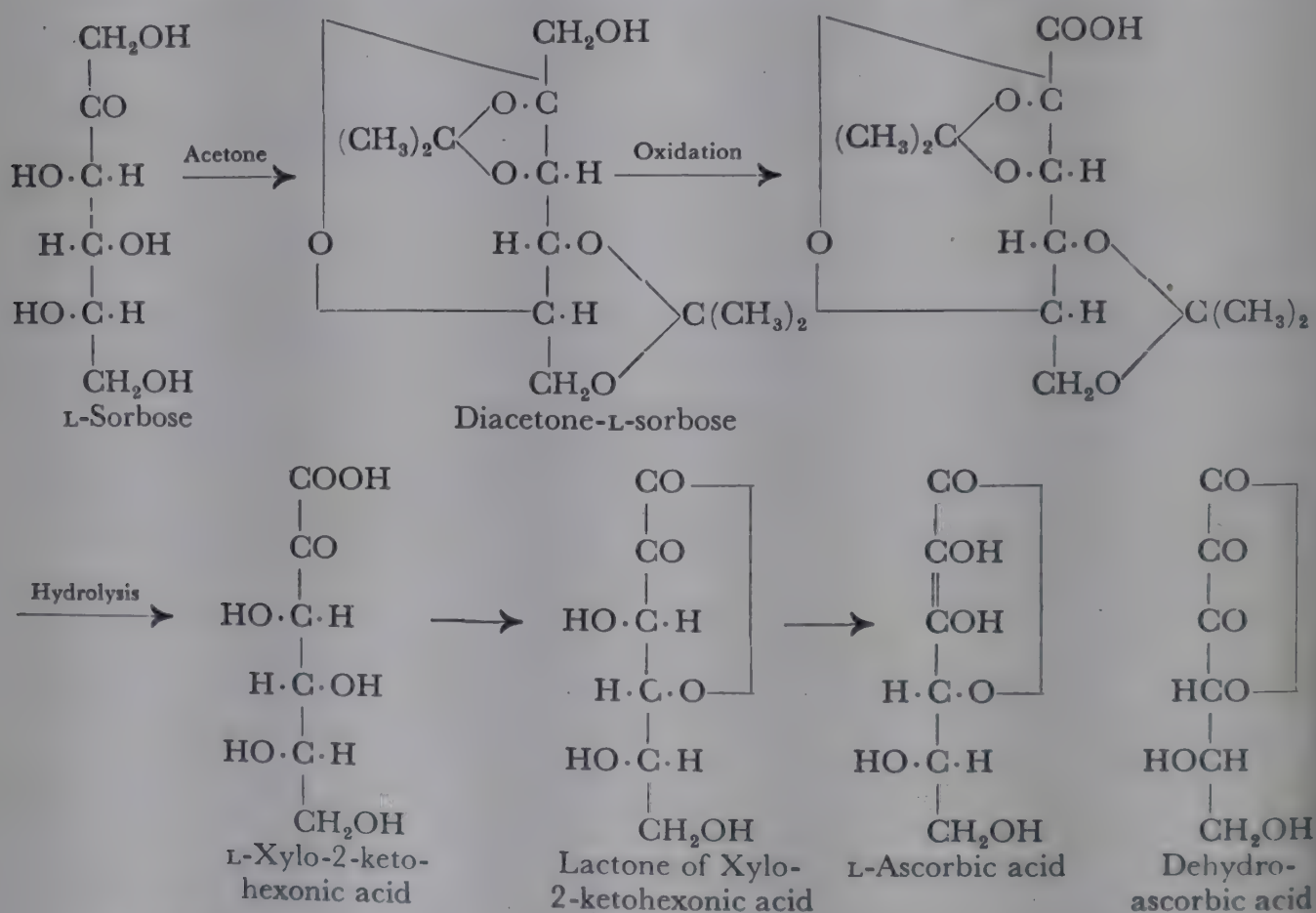
VITAMIN C, the antiscorbutic vitamin, is likewise soluble in water. It is found particularly abundantly in fresh fruits (oranges, lemons, black-currants, and also in species of cabbage, beans, etc.). Vitamin C in solution is very sensitive to atmospheric oxygen and heat, and is the most easily destroyed of all known vitamins.

Also this vitamin has been known in the pure state for some years. It was first obtained in the crystalline form from the adrenal cortex by Szent-Györgyi, and was later called *L-ascorbic acid*. Its molecular formula is $\text{C}_6\text{H}_8\text{O}_6$. The investigation of its structure, to which especially Haworth, Hirst, Karrer, and Micheel contributed, led to the following structural formula (Haworth, Hirst, von Euler):



L-Ascorbic acid was the first vitamin to be prepared by total synthesis. Several processes are now known for the synthetic preparation of vitamin C and analogous compounds (Reichstein, Haworth, and Hirst).

The method used technically starts from L-sorbose, which can be obtained from sorbitol by oxidation by means of the sorbose bacterium (cf. p. 347). L-Sorbose is converted into the diacetone derivative, the latter is oxidized to the carboxylic acid, and the acetone residues are removed by acid hydrolysis. L-Xylo-2-ketohexonic acid and its lactone are thus produced, which is tautomeric with L-ascorbic acid, and is converted into the latter by boiling with dilute acids:

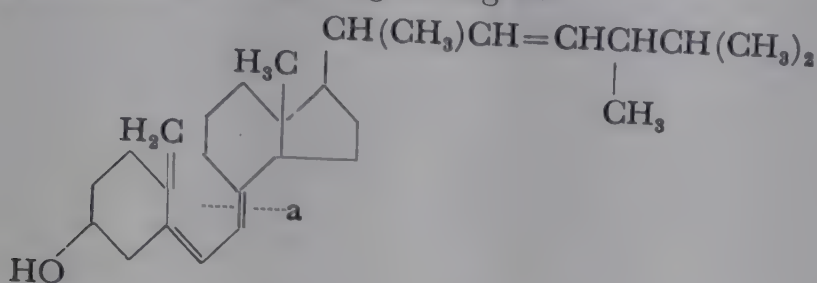


In the ascorbic acid molecule there are two enol groups, which cause the acidity of the compound. It forms neutral, soluble monoalkali salts. Its exceedingly powerful reducing action is to be specially noted. Ascorbic acid is dehydrogenated even by weak oxidizing agents, dehydroascorbic acid being the first oxidation product. It can be reduced again to ascorbic acid. Stronger oxidizing agents give rise to extensive decomposition of the molecule.

VITAMIN D, antirachitic fat-soluble vitamin, occurs in the liver. Before it could be isolated and more closely studied, an antirachitic principle differing from liver-oil vitamin D was obtained by irradiating ergosterol with ultra-violet

light (Windaus, Hess, Rosenheim). It could be separated in the pure and crystalline state from the crude products of the irradiation (Bourdillon and co-workers; also Linsert and Windaus). The crystalline preparation is called *calciferol* (or vitamin D₂). It melts at 115–116°, and has specific rotation, $[\alpha]_D^{20} = +82.6^\circ$, in acetone.

Calciferol is isomeric with ergosterol, and therefore possesses the molecular formula $C_{28}H_{43}OH$. It contains four double bonds. According to the investigations of the Windaus school it has the following constitution. According to this it is formed from ergosterol by the opening of ring B:



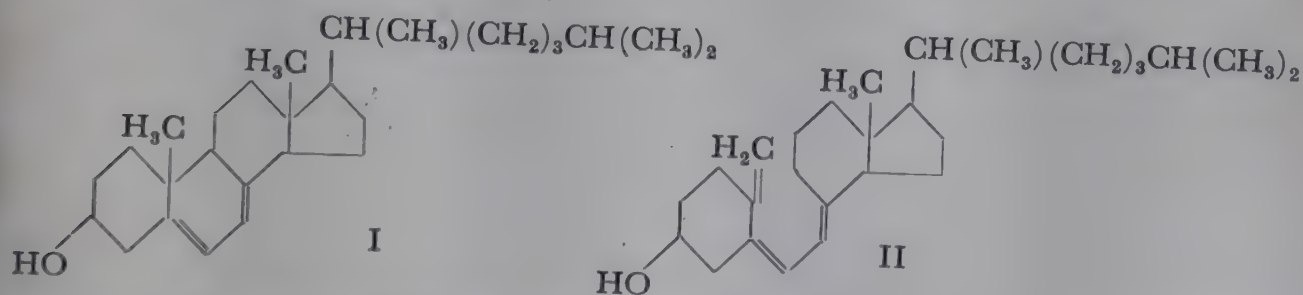
Calciferol can be oxidized to a ketone, $C_{19}H_{34}O$ (fission at á). The transformation of ergosterol to calciferol is shown in the following scheme:

The transformation of ergosterol by light is a very complicated process, leading to the successive formation of various irradiation products. This photochemical series comprises the following compounds:

Ergosterol \longrightarrow lumisterol \longrightarrow (protachysterol) \longrightarrow tachysterol \longrightarrow vitamin D₂ \longrightarrow toxisterol and suprasterols I and II.

The separation of these compounds is troublesome. Lumisterol is probably a stereoisomeric form of ergosterol, whilst in tachysterol as in calciferol, ring B of the sterol skeleton is split open.

Vitamin D from liver oil, *vitamin D₃*, is closely related to the irradiation product of ergosterol. It has been isolated by Brockmann from tunny-liver oil, but also occurs in other animals (pigs, etc.). Vitamin D₃ is derived from 7-dehydrocholesterol (I), from which it can be produced synthetically by exposing it to ultra-violet light. Windaus and his co-workers ascribe to it the formula (II), which differs from that of calciferol in the nature of the side chain (containing one methyl group and one double bond less):



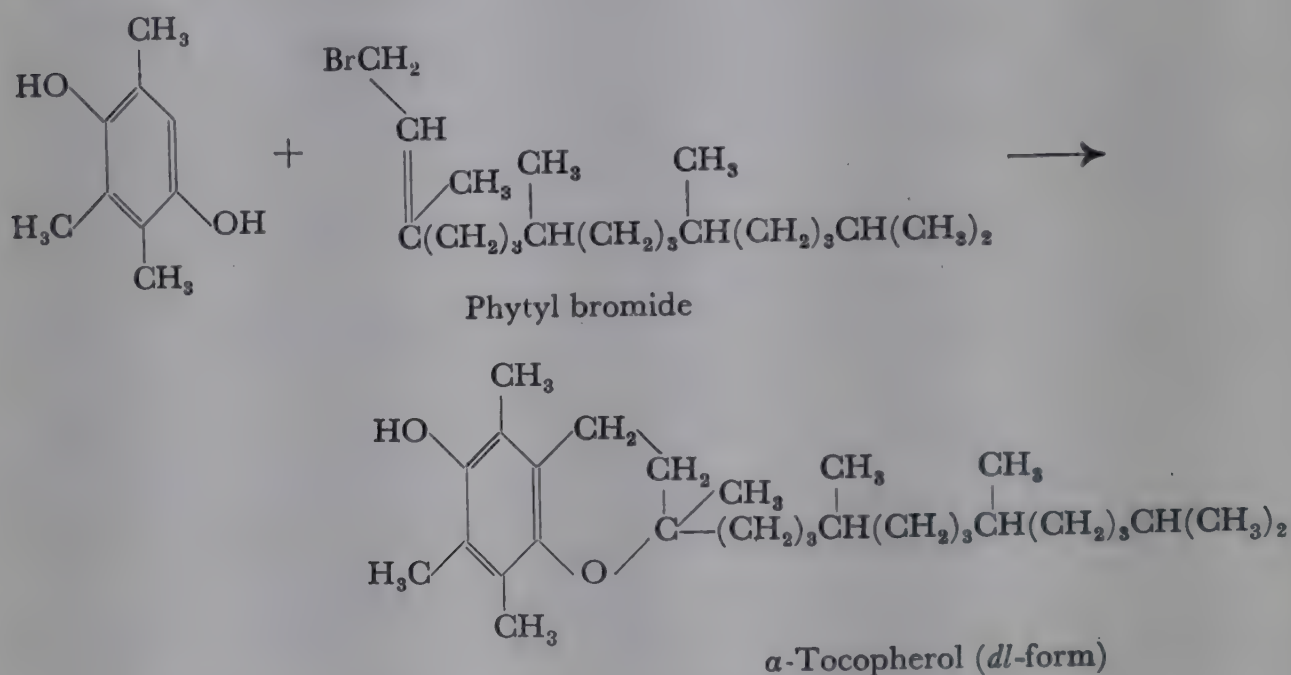
Both calciferol (vitamin D₂) and vitamin D₃ have a strong antirachitic activity. The relative potency of the two substances, however, varies greatly with different species of animal.

Finally, it has been possible by irradiation of 22-dihydroergosterol to prepare a vitamin D₄, which differs from calciferol in constitution only in that the double bond in the side chain is absent. Vitamin D₄ has likewise an antirachitic action, but is less active than vitamins D₂ and D₃.

Dihydrotachysterol (trade name "A.T. 10") is used in medicine to cure post-operative tetany. The pure compound melts at 125–127°; the trade product contains about 30 % dihydrovitamin D₂.

VITAMIN E is a fat-soluble vitamin which is necessary for reproduction (anti-sterility vitamin). Evans, Emerson, and Emerson have isolated two alcohols, α - and β -tocopherol, which have the formulæ $C_{29}H_{50}O_2$ and $C_{28}H_{48}O_2$, respectively, from wheat-germ oil and other vegetable oils. These alcohols are themselves oils, but form well-crystallized allophanates, *p*-nitrophenylurethans, and other esters. Both tocopherols possess vitamin E activity, 3 mg doses of the α -compound, and 8 mg of the β -compound being sufficient to render rats fertile. Deficiency of vitamin E in female animals makes them incapable of bearing live offspring.

The elucidation of the constitution of the tocopherols is based chiefly on the work of E. Fernholz, W. John, P. Karrer, and A. R. Todd, and has been finally settled by the total synthesis of *dl*- α -tocopherol by P. Karrer and his co-workers. Trimethylhydroquinone was condensed with phytol bromide (obtained from phytol) with the addition of a catalyst (e.g. $ZnCl_2$). The course of the reaction is expressed by the following formulæ:

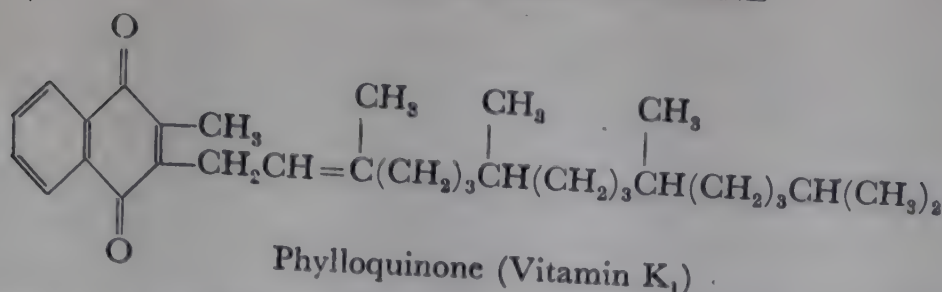


α -Tocopherol is thus 2:5:7:8-tetramethyl-2-[4':8':12'-trimethyl-tridecyl]-6-hydroxychroman. In β -tocopherol (also known as cumotocopherol or neotocopherol) there are only two methyl groups substituted in the benzene ring (positions 5 and 8).

VITAMIN K. This vitamin, equally indispensable to man and animals, regulates the coagulation of the blood. Deficiency of vitamin K leads to a decrease of prothrombin (one of the factors involved in the coagulation of blood) in the body. Dam as well as Almquist have proved the existence of such a factor by experiments on animals.

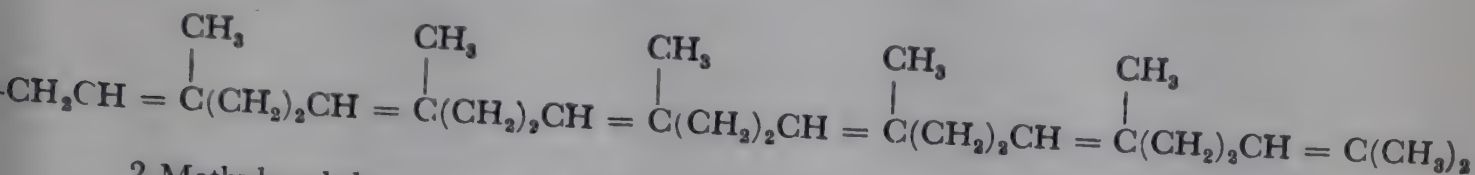
So far, two natural K vitamins are known. The one, *vitamin K₁* or *phylloquinone*, is found in green plants and was isolated for the first time from alfalfa (P. Karrer); the other, *vitamin K₂*, occurs in bacteria and was obtained from rotting fish meal (Doisy).

Phylloquinone is a yellow viscous oil. Its constitution is that of 2-methyl-3-phytyl-naphthaquinone-(1:4) (Doisy). It has been artificially prepared from 2-methyl-naphthahydroquinone and phytol or phytol bromide and a catalyst (Fieser):



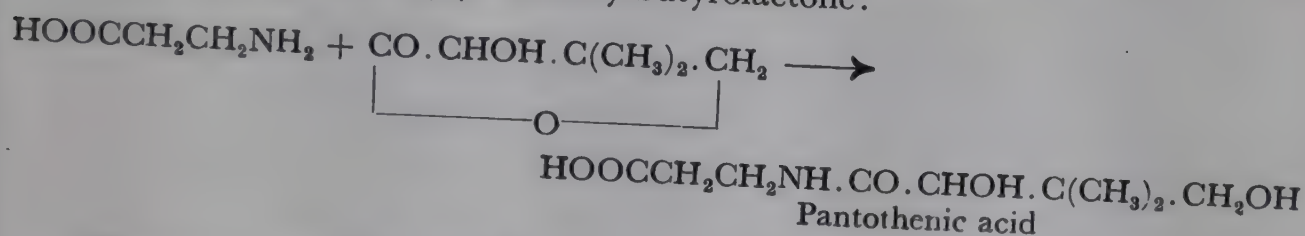
It proved to be very sensitive to light, as well as to alkali which changes phylloquinone into phthiocol (see p. 588), with fission of the phytyl residue.

The constitution of vitamin K₂ which melts at 51°, differs from that of phylloquinone in that the phytyl residue in the preceding formula of phylloquinone is replaced by the following side chain:



2-Methylnaphthaquinone-1:4 and some related compounds possess the same physiological effect as the vitamins K₁ and K₂.

PANTOTHENIC ACID. Pantothenic acid, discovered by R. J. Williams (who also elucidated its structure), is a very widely distributed, water-soluble growth-factor, which appears to be indispensable for both man and higher animals, and can therefore be regarded as a vitamin. The compound is N-[α,γ -dihydroxy- β,β -dimethylbutyryl]- β -alanine and can be easily prepared from β -alanine (or its ester) and α,γ -dihydroxy- β,β -dimethylbutyrolactone:

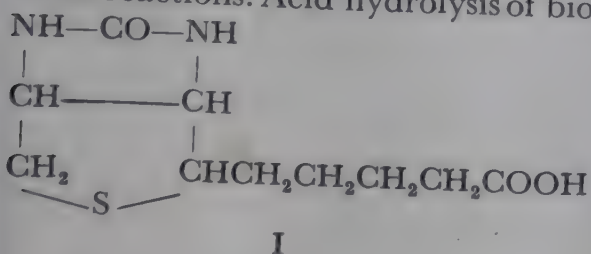


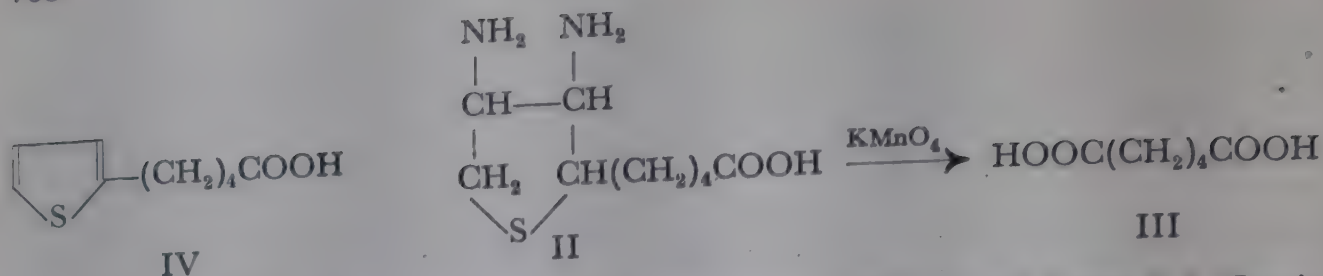
Pantothenic acid belongs to the water-soluble, B-vitamins. The naturally occurring form, and the only one which is biologically active is the *l*-compound.

BIOTIN. One of the last water-soluble vitamins to be discovered is *biotin*. It is found widely spread in the vegetable kingdom, as well as in animal and human organs, but always in very low concentration. Kögl succeeded in isolating it from egg yolk; later, the compound was also obtained by du Vigneaud and co-workers in a pure state from liver and other material.

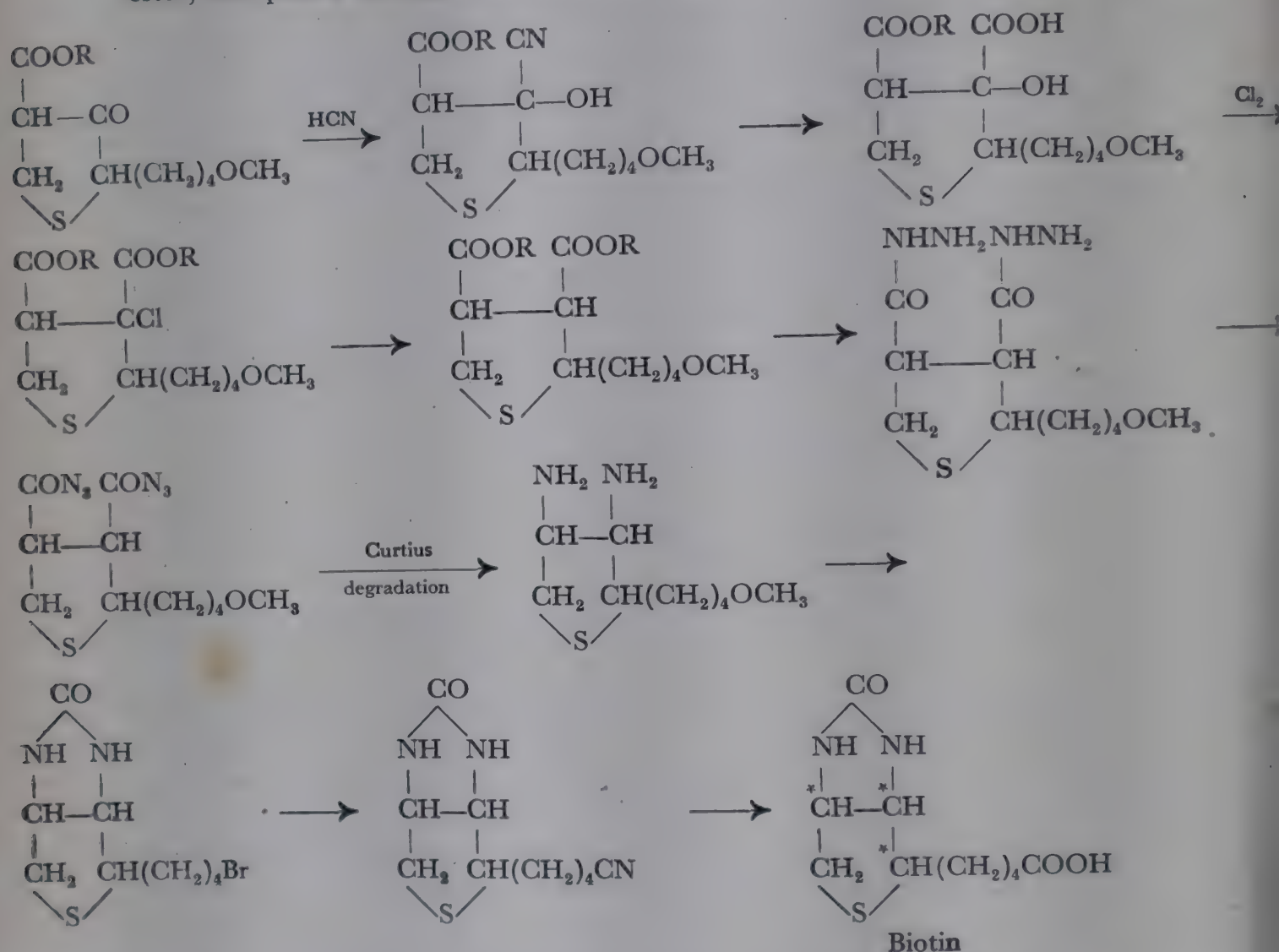
It is not yet certain whether egg-biotin and liver-biotin are identical; Kögl denotes the former as α - and the latter as β -biotin. The following details refer to " β -biotin", which has been the more thoroughly investigated.

Biotin is a compound containing sulphur, and is soluble in water. It has the formula I given below. This formula has been derived from the study of degradation reactions. Acid hydrolysis of biotin produced the diaminocarboxylic acid (II), which, by oxidation with KMnO_4 gave adipic acid (III), and by means of the Hofmann degradation yielded δ -carboxybutylthiophen (IV); the latter compound proved to be identical with a synthetic preparation:





Different syntheses of biotin have been accomplished; one is by S.A. Harris and co-workers, and another by A. Grüssner, J. P. Bourquin and O. Schnider. The latter one starts from 2-(ω -methoxybutyl)-3-keto-thiophan-4-carboxylic acid ester, and passes through the following stages:



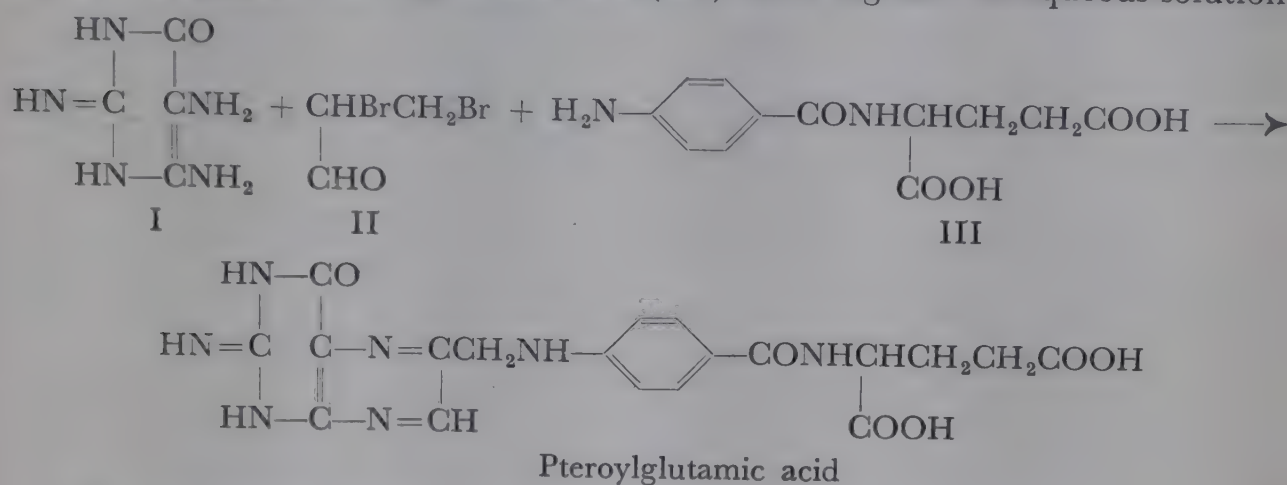
Biotin contains 3 asymmetric C-atoms, and may occur, therefore, theoretically, in 8 stereoisomeric forms. In addition to natural biotin, which has also been produced artificially from *dl*-biotin, obtained synthetically, stereoisomers appear during the biotin syntheses (*dl*-epibiotin, *dl*-allobiotin, and *dl*-epiallobiotin). Natural biotin is dextrorotatory. Its two rings are fused in the *cis*-position. Biotins differ from *epibiotins* in the configuration of the α -C-atom of the thiophan ring; *allo*- and *epiallobiotin* have the rings arranged in the *trans*-position. These stereoisomers of biotin apparently have no biological activity.

Biotin is indispensable to many micro-organisms as a growth-factor. Whether it is also important in the higher animals and man is not yet quite clear. In egg-white there occurs an antagonist to biotin, *avidin*, which nullifies the action of the

former, and can, in experiments on animals, cause a biotin-avitaminosis (skin injury, falling out of hair, changes in blood-picture). Avidin is a high-molecular compound and appears to be related to the proteins.

PTEROYLGLUTAMIC ACID, or FOLIC ACID. (*Lactobacillus casei* factor). This vitamin is widely distributed in plants and occurs, for example, in all green leaves. It is an essential accessory dietary factor for man and animals, and also for some micro-organisms.

The compound has been isolated, for example, from liver and *Coryne bacteria*. Moreover, several synthetic methods of preparation are known, by which to-day pteroylglutamic acid is produced technically. Thus it is formed (in about 15% yield) when 2:4:5-triamino-6-hydroxypyrimidine (I), α,β -dibromopropionaldehyde (II), and *p*-aminobenzoylglutamic acid (III) react together in aqueous solution:



The compound is, therefore, a pteridine derivative, i.e. a pterin (q.v.). It is rather difficultly soluble in water, and readily soluble in alkalis.

Pteroylglutamic acid possesses a certain curative action in pernicious anæmia and is used therapeutically.

Compounds related to folic acid have also been found in organisms (e.g. in yeast). These differ from folic acid in that the glutamic acid residue is replaced by a polypeptide composed of 3–10 glutamic acid molecules. These pteroyl polyglutamates have, in part, different physiological actions.

Rubber¹

Rubber (caoutchouc) is, on account of its excellent elastic properties, an indispensable product for modern industry, and finds application in enormous quantities for a great variety of purposes (manufacture of tubes, tyres, toys, vulcanite articles). It occurs in the latex of various tropical trees of the *Euphorbiaceæ*, *Apocynaceæ*, and *Moraceæ* families. In practice, rubber is produced almost exclusively from trees of the species *Hevea brasiliensis*, which are indigenous to Brazil.

The latex obtained from these trees consists of ca. 55–60% water and 35–40% rubber. The latter is present in the form of small globules which are stabilized by

¹ See C. D. HARRIES, *Untersuchungen über die natürlichen und künstlichen Kautschukarten*, Berlin, (1919) — B. D. W. LUFF, *Chemistry of Rubber*, (1924). — R. DIEMAR, *Die Synthese des Kautschuks*, Dresden-Leipzig. — S. BOSTRÖM *et al.*, *Kautschuk und verwandte Stoffe*, Berlin, (1940). — H. P. and W. H. STEVENS, *Rubber Latex*, London, (1936). — C. W. BEDFORD and H. A. WINKELMANN, *Systematic Survey of Rubber Chemistry*, New York, (1923). — C. C. DAVIS and J. T. BLAKE, *The Chemistry and Technology of Rubber*, New York, (1937). — K. MEMMLER, *The Science of Rubber*, English translation by R. F. Dunbrook and V. N. Morris, New York, (1945).

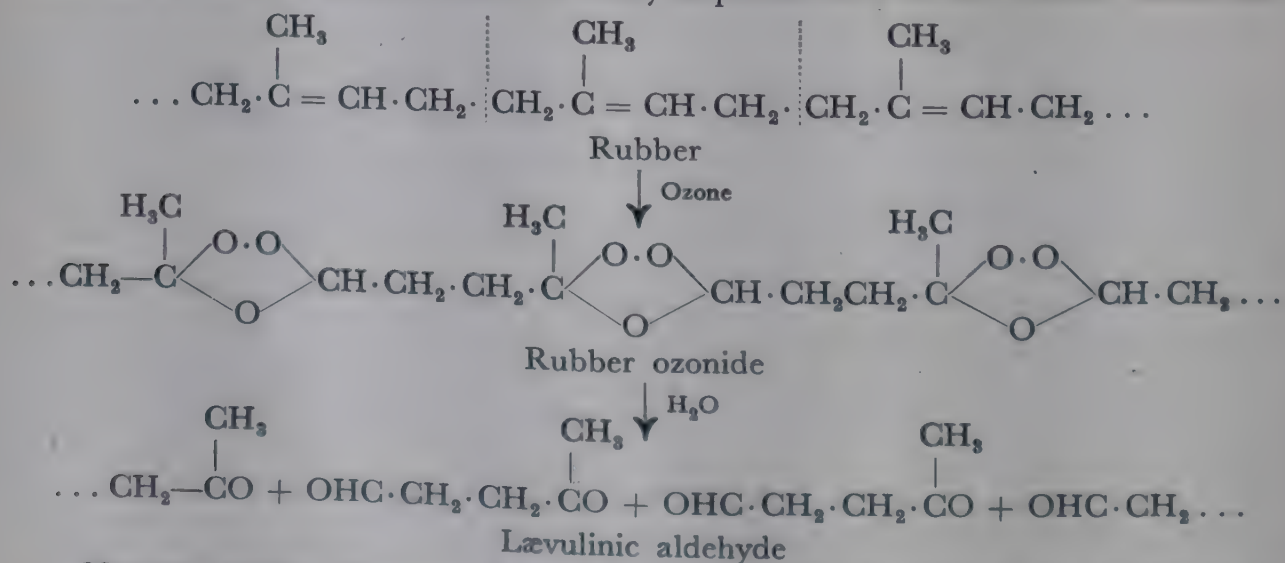
a protein layer adsorbed on their surface. Part of the latex, after having been protected against fermentation by addition of some ammonia, is exported as such to industrial countries. Another part is worked up at the place of its origin to give solid rubber. In the latter case, the minute rubber particles are coagulated by addition of acetic acid or formic acid, and the coagulum obtained is thoroughly pressed out by metal rollers. Finally the thin rubber sheets are dried in the air or over open fires.

Natural, pure rubber is a readily oxidizable substance, being however somewhat protected by "impurities", particularly amines. These originate from the proteins present in the latex and act as antioxidants. It does not, however, retain its original elasticity indefinitely. It slowly becomes hard and brittle. On the other hand it is possible by a special treatment, known as *vulcanization*, to retain the valuable elastic properties of the rubber. The principle of the various processes for vulcanization is the addition of sulphur to the rubber. This probably forms solid solutions with rubber in the initial stages, and can then be easily extracted again, but it slowly becomes chemically combined with the rubber molecule.

In *cold vulcanization* the rubber material is placed in solutions of sulphur monochloride in carbon disulphide. The method of *hot vulcanization* is more largely used at present. The rubber is mixed with sulphur and then heated to 135–140°, usually directly in steam-heated presses. By this treatment the rubber loses its sensitivity towards atmospheric conditions, and its capability of resistance and its elasticity improve.

CONSTITUTION. Rubber can be regarded as the final member of a series of compounds starting from isoprene (hemiterpene), and passing through the terpenes, sesquiterpenes, diterpenes, etc. All these compounds are polymerization products of isoprene.

The genetic connection between rubber and the lower terpenes follows on the one hand from the fact that rubber breaks down into isoprene, dipentene, and other terpenes on dry distillation, and on the other from the fact that isoprene can be polymerized, when suitably treated, to rubber-like products. An important piece of work for the determination of the constitution of rubber was the investigation of the action of ozone on the substance. Harries showed that rubber was converted into lævulinic aldehyde (and lævulinic acid) by this process. It follows that there must be a normal chain of many isoprene units in the rubber molecule:



Natural rubber, however, is not a homogeneous substance, but a mixture of related hydrocarbons of high molecular weights. The average molecular weight

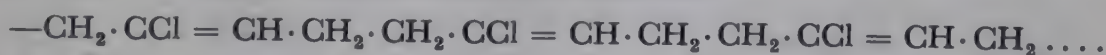
can be approximately determined from the viscosity of rubber solutions and from their osmotic pressures. These measurements show that hundreds of isoprene units are contained in the rubber molecules.

At low temperatures rubber gradually becomes crystalline; a crystalline phase is also obtained on stretching the substance (Katz). From X-ray diffraction studies of crystalline rubber it has been concluded that it exists in the *cis*-configuration; gutta-percha has been found to have the *trans*-configuration.

SYNTHETIC RUBBER. The industrial value of rubber, and the steadily increasing demand for this product year by year, has inspired attempts to produce rubber synthetically, which have been carried on for some time. It has been possible to devise methods by which the polymerization of isoprene, and its lower and higher homologues, butadiene and dimethylbutadiene, into rubber-like products can be effected. According to F. Hofmann the process can be carried out by prolonged heating (10–14 days) of the butadiene hydrocarbons under pressure to about 95°. Various substances, such as sulphur, organometallic compounds, starch, proteins, etc., have a catalytic influence. Butadienes are also converted into rubber-like masses on long keeping (Kondakow). Sodium (in the presence of carbon dioxide) also acts as a polymerizing agent. In recent times, synthetic rubbers (so-called "Buna" rubbers) have been made on an industrial scale in Germany from butadiene, which itself is made from acetylene. The polymerization can be effected by sodium (Buna 115), or by shaking a butadiene-acrylonitrile emulsion in water thus producing a mixed polymer (Buna N, Perbunan, and Hycar). By mixed polymerization of butadiene and styrene, the polymerizate Buna S, is obtained. The various polymerization products differ considerably in their properties.

As regards the constitution, synthetic isoprene rubber differs from natural rubber in its less regular structure. This is due to the fact that isoprene and the other dienes can polymerize not only by reaction in the 1:4-positions, but also in the 1:2- and 3:4-positions, thus leading to branching of the carbon chains.

In the United States, rubber-like products have been obtained by Carothers from the readily accessible 2-chlorobutadiene, which also goes under the name of *chloroprene*, and can be made from acetylene. The products resemble natural rubber in their properties, and are even superior to it in certain respects (e.g. oil-resistance). Chloroprene rubber (Duprene, Sovprene) probably consists of a regular chain of linked chlorobutadiene residues:



Chloroisoprene yields similar polymerization products. Some of these chlorinated rubbers become crystalline on stretching. A good rubber (Oppanol, Vistanex) has also been produced recently by polymerization of *isobutylene*, $\text{CH}_2 = \text{C}(\text{CH}_3)_2$. Owing to the lack of double bonds it cannot be vulcanized. It is, however, possible to obtain a vulcanized product, if a mixed polymerizate is prepared from *isobutylene* and 3% isoprene or butadiene, which contains the necessary double bonds. Oppanol is more stable towards oxygen than natural rubber.

GUTTA-PERCHA and BALATA are products which resemble rubber fairly closely in chemical composition, but differ from it in their physical properties. At ordinary temperatures they are tough, hard, and not very elastic, but they become soft in hot water. Their good crystallizability is noteworthy and exceeds considerably that of rubber. Gutta-percha has considerable importance as an insulator for electrical cables. Driving belts for machines are made of cotton impregnated with balata. These substances are also obtained from the latex of tropical trees, and contain considerable quantities of resins and other impurities.

CHAPTER 57

CYCLOHEPTANE AND ITS DERIVATIVES

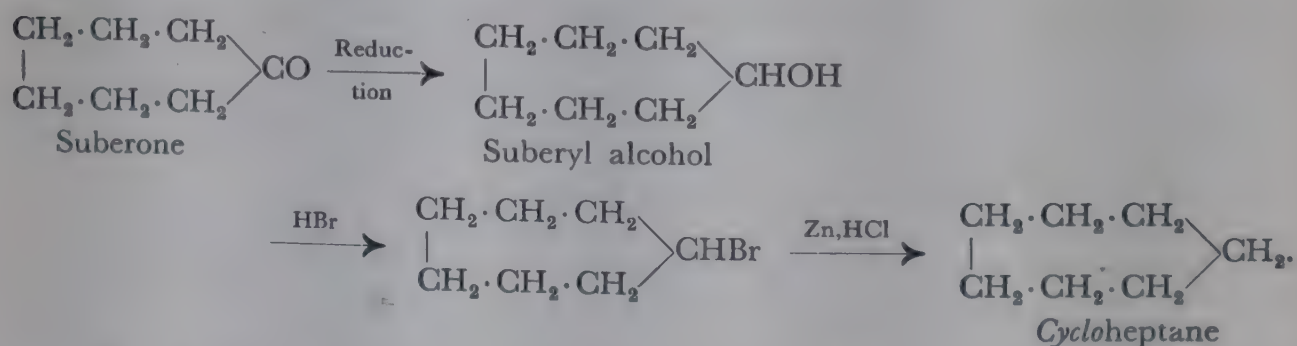
The synthetic preparation of *cycloheptane* and *cyclooctane* derivatives presents considerably greater difficulty than the preparation of carbocyclic compounds with five- or six-membered rings. The "strain theory" of A. von Baeyer, already mentioned before on several occasions, ascribes this to a condition of greater strain, which would be caused in the higher ring systems by the greater deviation of the carbon valencies from their natural positions. This explanation is considered with increased scepticism at present. If the carbon atoms in the *cycloheptane*, *cyclooctane*, etc. rings are not all in one plane, but are distributed in two or more planes, such rings could be completely strainless (Mohr).

The experimental investigation of the spatial structure of carbocyclic rings has led to numerous observations which can only be explained by supposing a non-planar structure for such carbon rings. As examples may be mentioned the existence of *trans*-hexahydrophthalic anhydride (p. 692), and the discovery by W. Hückel of the existence of four isomeric decahydro- β -naphthols (p. 408).

Further evidence is supplied by the syntheses of carbocyclic rings with up to 30 carbon atoms. It would be impossible to have a planar arrangement of the carbon atoms in these rings, as the strain in these molecules would be so great that the capability of existence of such structures would appear improbable.

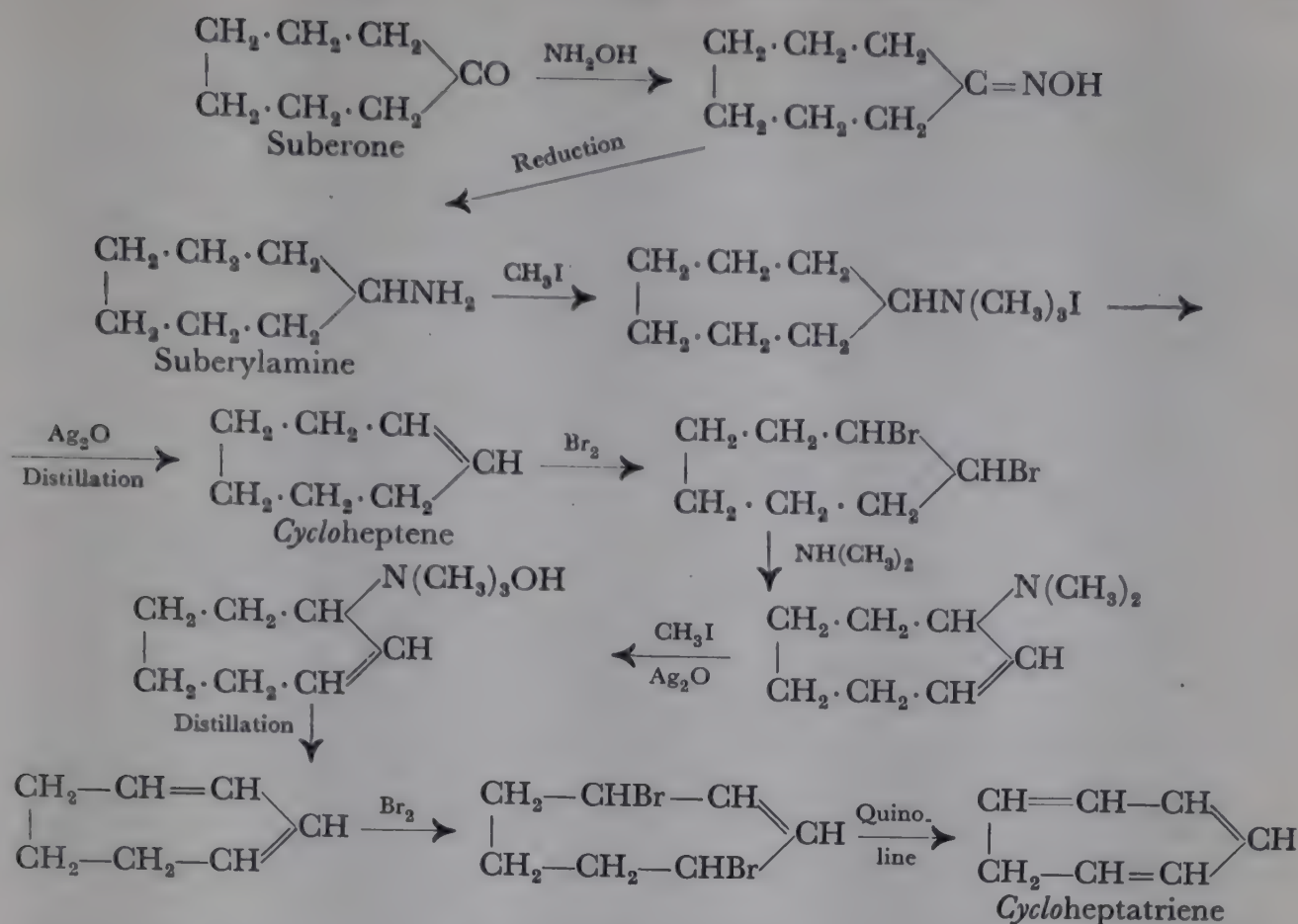
A method of obtaining a *cycloheptane* derivative is the dry distillation of calcium suberate. *Cycloheptanone*, or *suberone* (b.p. 180°), is thus obtained. It has an odour like peppermint.

Cycloheptanone is a suitable substance from which to prepare other *cycloheptane* compounds. By reduction it is converted into *cycloheptanol* (suberyl alcohol), from which *cycloheptyl* bromide can be obtained, and reduction of the latter, *cycloheptane* has been produced (Markovnikov):

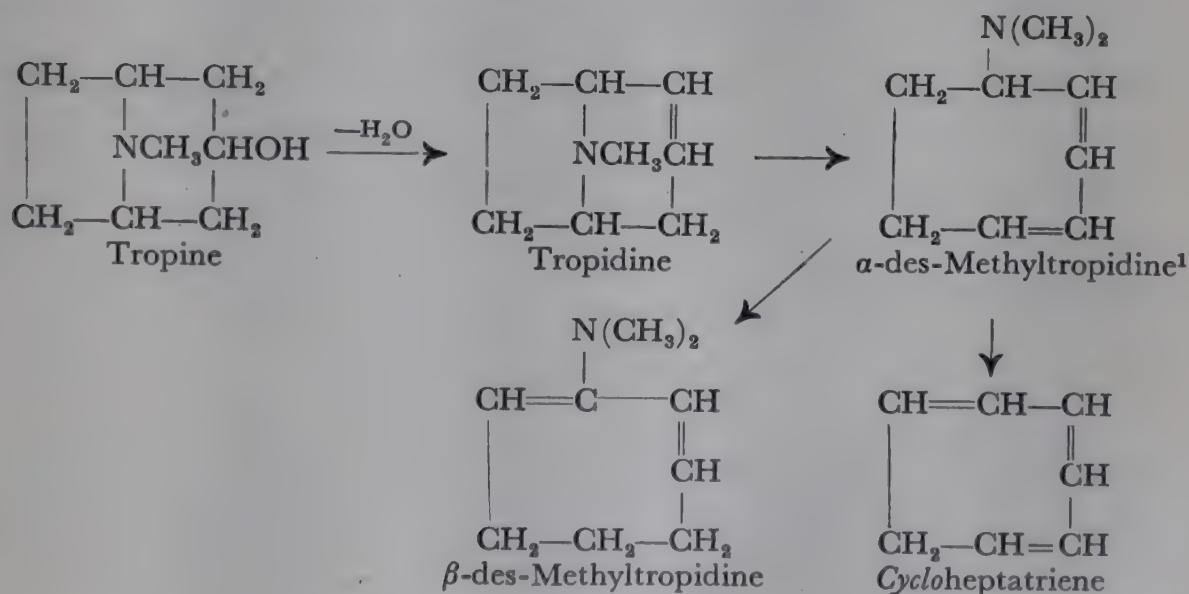


If *cycloheptane* is passed over reduced nickel at high temperatures (235°), or if it is strongly heated with hydriodic acid, ring contraction occurs with formation of methyl*cyclohexane* and dimethyl*cyclopentane*. For this reason suberone cannot be directly reduced with hydriodic acid to the hydrocarbon.

Among the unsaturated hydrocarbons of the *cycloheptane* series, *cycloheptatriene* (*tropilidene*) was first prepared by Ladenburg and Merling by the exhaustive methylation of tropidine (see Ch 67, 1). The nature of the hydrocarbon, however, was recognized only after the elucidation of the constitution of tropine by Willstätter, who also accomplished the systematic degradation of *cycloheptanone* to *cycloheptene*, *cycloheptadiene*, and *cycloheptatriene*, as follows:



In the degradation of the alkaloid tropine to *cycloheptatriene*, the nitrogen is eliminated in a similar way as in the above series of reactions, i.e. by exhaustive methylation and distillation of the quaternary ammonium base:



On heating α -des-methyltropidine, isomerization to β -des-methyltropidine occurs with migration of a double bond. The latter base loses nitrogen when attempts are made to methylate it (ethylenic linkage adjacent to the nitrogen!).

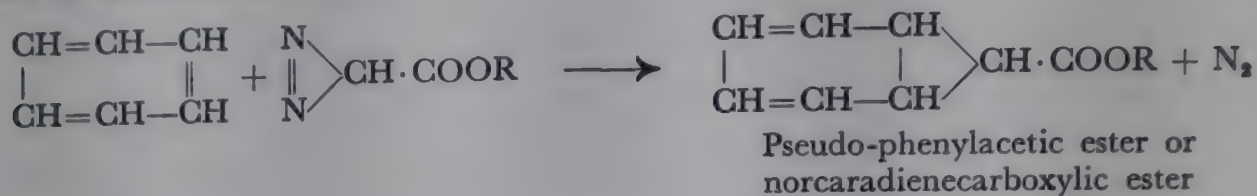
Cycloheptadiene, and particularly *cycloheptatriene*, are unstable hydrocarbons. The latter resinifies rapidly in the air:

¹ Unsaturated amines produced from cyclic ammonium bases by the Hofmann degradation, with rupture of the ring, are distinguished from their cyclic isomerides by the prefix "des" (corresponding to the Latin "dis" and the French "dés"). This terminology is due to A. von Baeyer and R. Willstätter.

<i>Cycloheptane</i>	b.p. 117°	<i>Cycloheptadiene</i>	b.p. 120–121°
<i>Cycloheptene</i>	b.p. 115°	<i>Cycloheptatriene</i>	b.p. 116°.

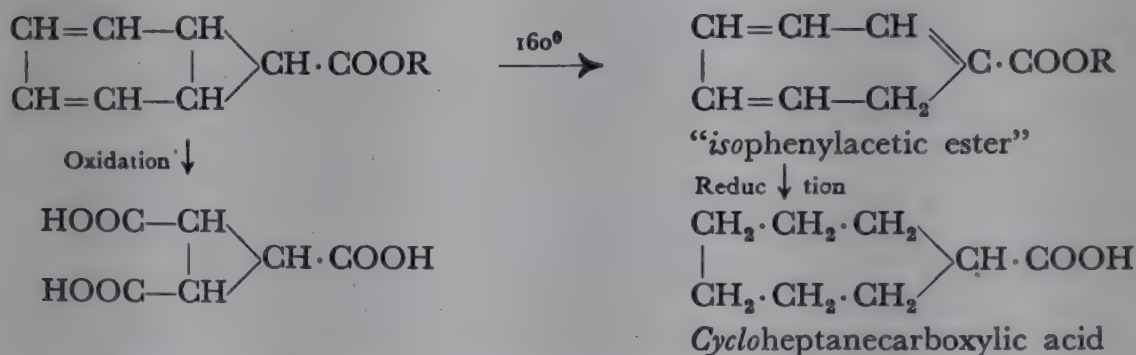
Another method of entering the *cycloheptane* series was discovered by Buchner. He found that diazoacetic ester condensed with benzene and other aromatic hydrocarbons (toluene, *p*-xylene) to bicyclic compounds, which contained a *cyclohexadiene* ring fused with a *cyclopropane* ring.

The reaction product with benzene and diazoacetic ester is *pseudo-phenylacetic ester* or *norcaradienecarboxylic ester*.

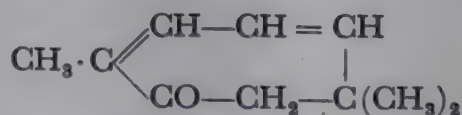


This ester is derived from the hydrocarbon *norcarane*, $\begin{array}{c} \text{CH}_2-\text{CH}_2-\text{CH} \\ | \quad \diagup \quad \diagdown \\ \text{CH}_2-\text{CH}_2-\text{CH} \end{array} \text{CH}_2$ (b.p. 110°), the name being connected with carone and carane (see p. 695).

By the oxidation of pseudo-phenylacetic ester, *cyclopropane*-1:2:3-tricarboxylic ester is produced. On heating to 160°, the former isomerizes to the ester of *cycloheptatrienecarboxylic acid* (*isophenylacetic ester*), which can be reduced to *cycloheptanecarboxylic acid*:

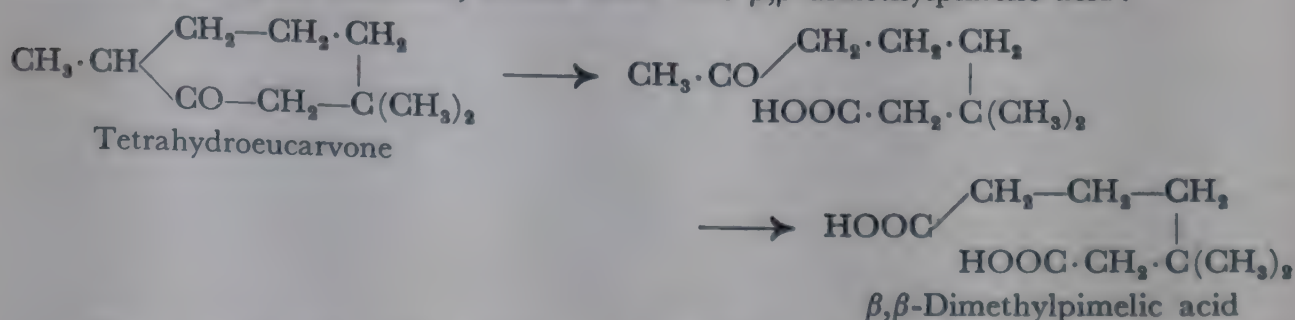


According to Wallach, *eucarvone* is also to be regarded as an unsaturated ketone of the *cycloheptane* series:



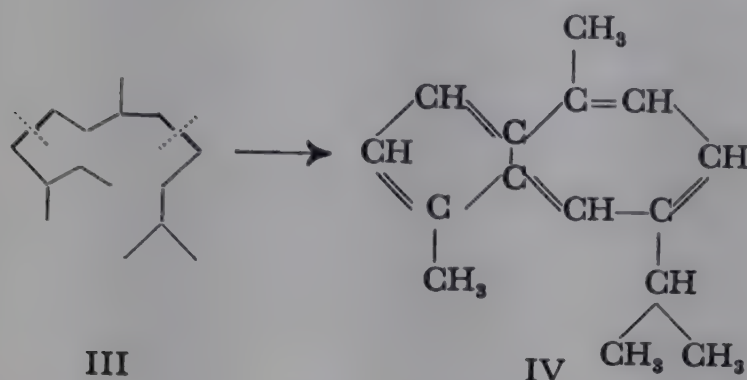
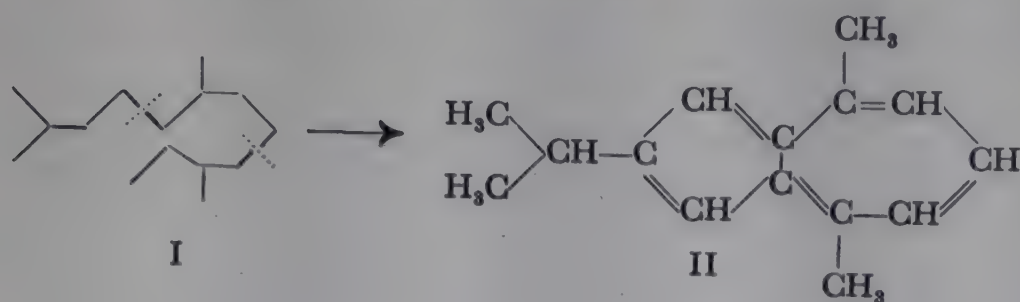
Its synthesis from carvone hydrobromide has been described on p. 686.

Eucarvone boils at 85–87° (12 mm). It can be catalytically reduced to tetrahydroeucarvone, which, on oxidation, breaks down into β,β -dimethylpimelic acid:

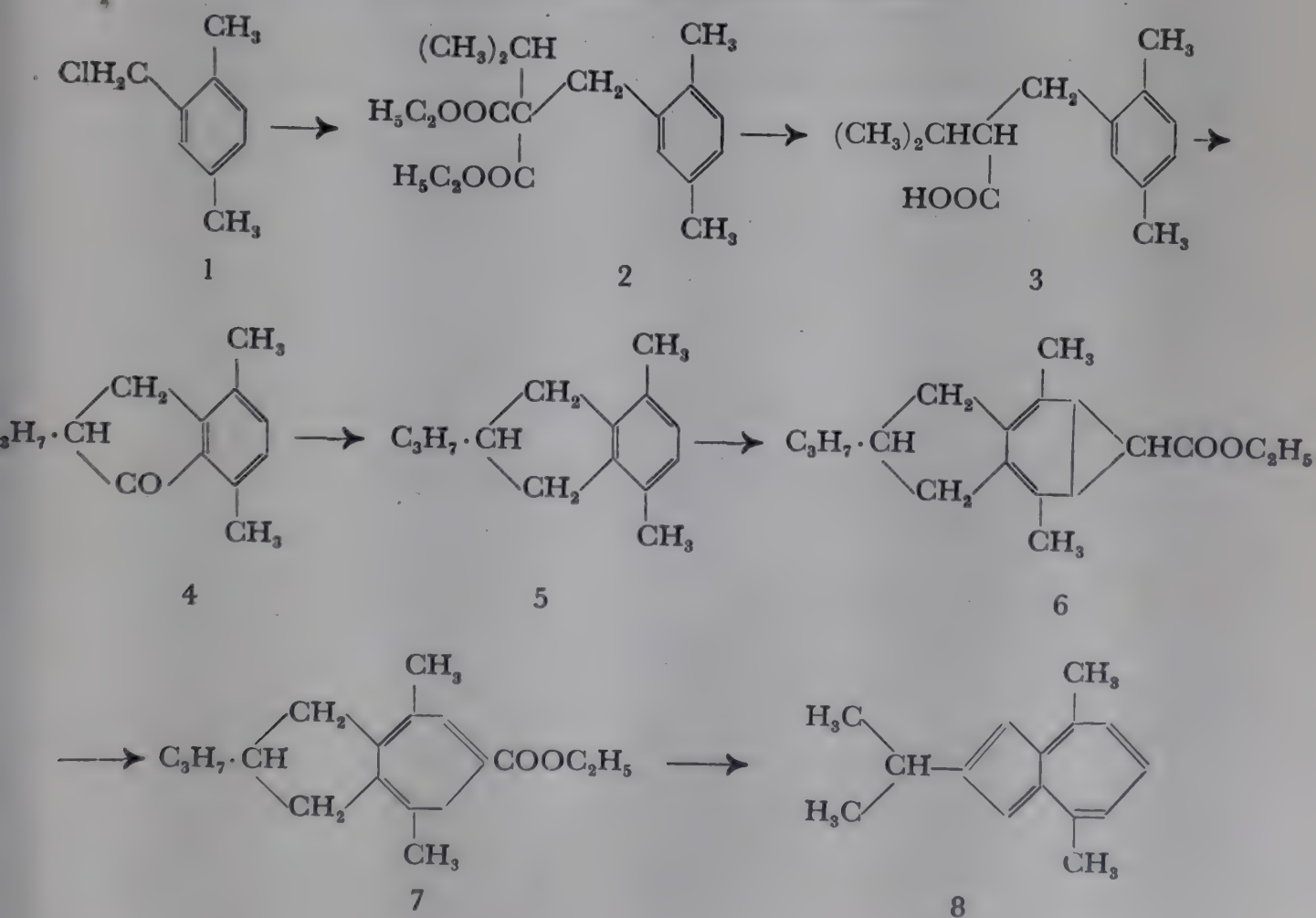


The *azulenes* have been shown by A. St. Pfau to be bicyclic compounds with a *cycloheptane* ring. These deep blue compounds are produced in different ways from sesquiterpenes, and also occur in nature. They are strongly unsaturated and

unstable. *Vetivazulene* (II), m.p. 32–33°, and *S-guaiiazulene* (IV) may be regarded, for example, as being derived from aliphatic sesquiterpenes (I and III).



It has also been possible to prepare vetivazulene synthetically (Pl. A. Plattner). The starting substances are 2-chloromethyl-*p*-xylene and sodioisopropylmalonic ester. The acid 3 of the formulæ below is converted into the ketone 4 *via* the chloride, and the latter is reduced to the hydrocarbon 5, which is then condensed with diazoacetic ester to the tricyclic carboxylic acid ester 6. When heated, compound 6 changes into 7, which gives vetivazulene on hydrolysis, decarboxylation, and dehydrogenation:



CHAPTER 58

CYCLOOCTANE AND ITS DERIVATIVES. ALICYCLIC COMPOUNDS WITH HIGHER RING SYSTEMS

The chemistry of *cyclooctane* is still very little developed, since the methods known up to the present for synthesizing *cyclooctane* derivatives give only poor yields.

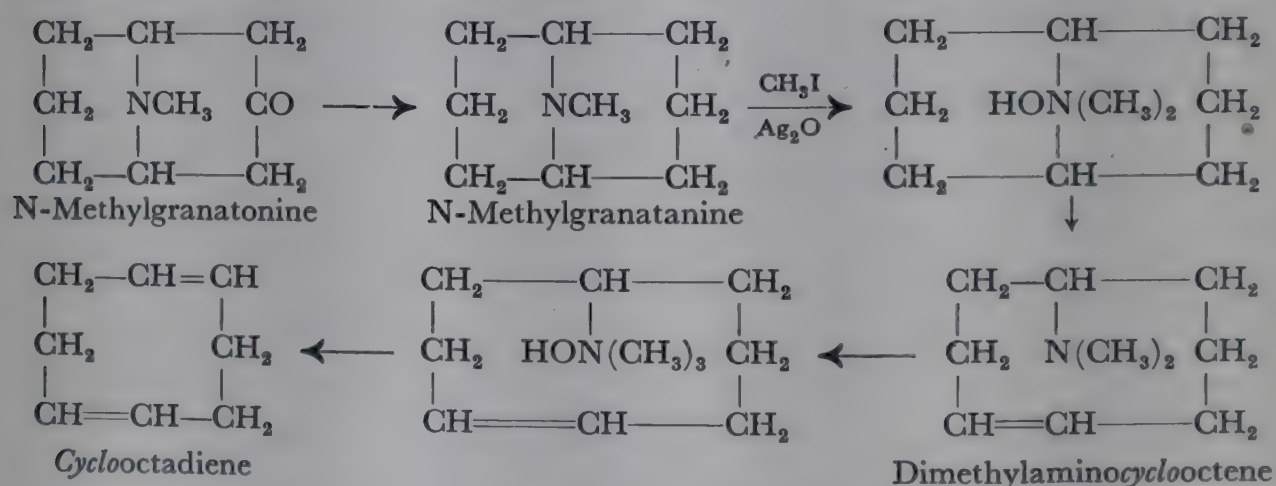
Cyclooctanone (*azelaone*) is formed in small quantities by the distillation of the calcium salt of azelaic acid:



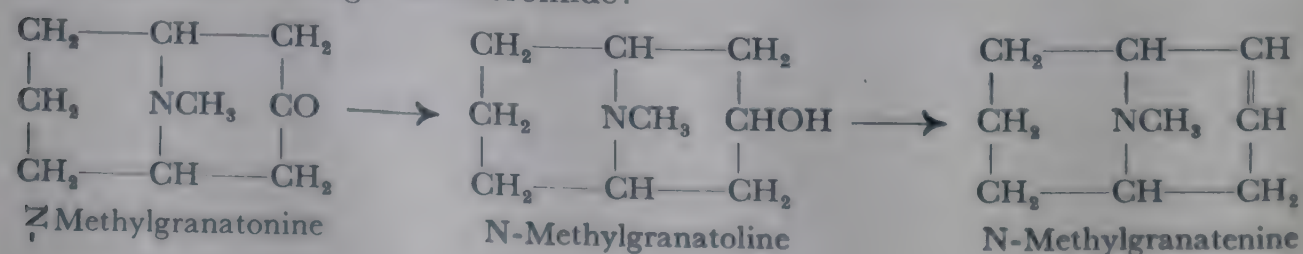
The ketone boils at 195–197°, and melts at 40–41°.

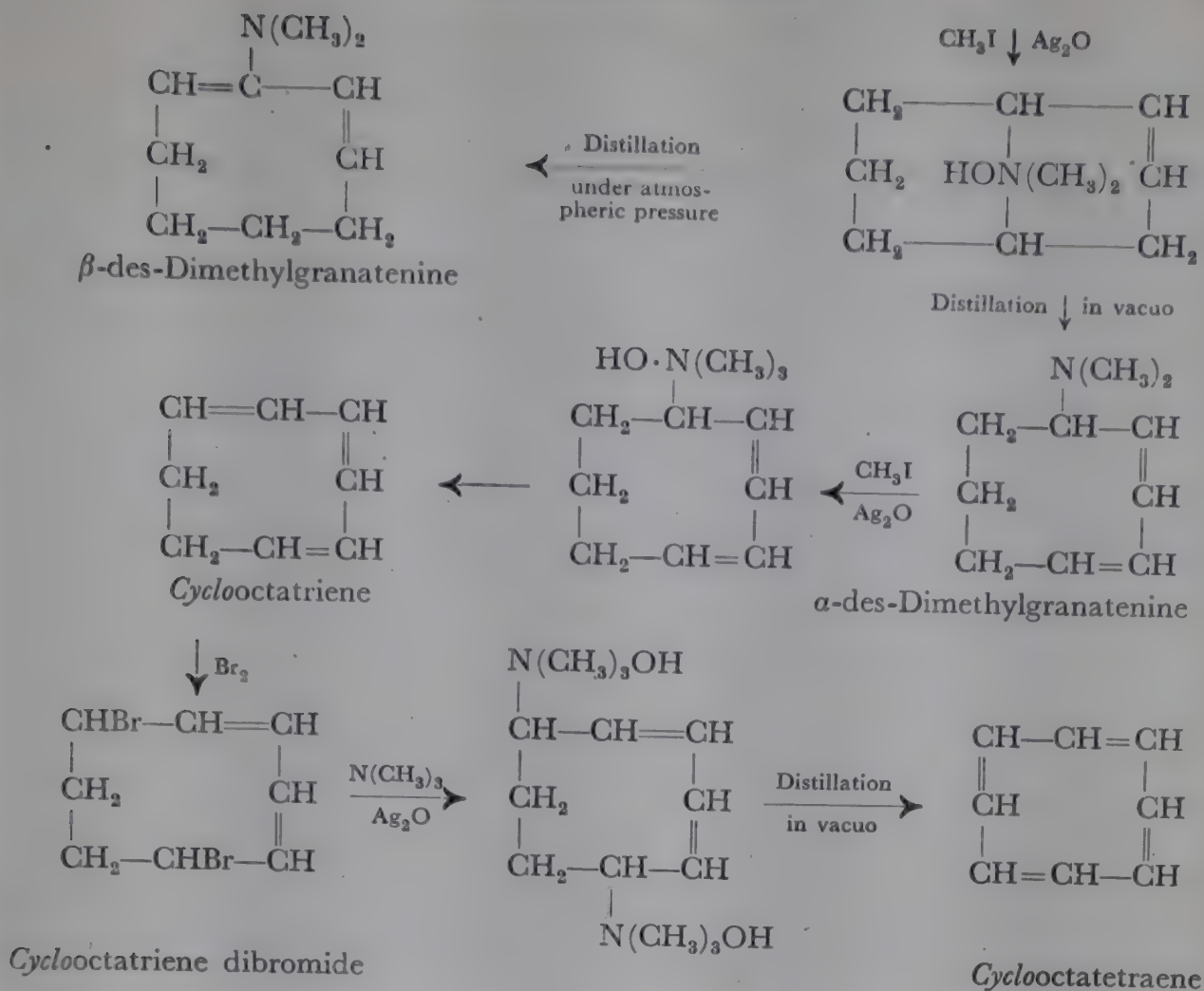
A suitable starting substance from which to prepare the saturated and unsaturated hydrocarbons of the *cyclooctane* series is the alkaloid *pseudopelletierine* (methylgranatonine) (Willstätter), of which the formula was established by the investigations of Ciamician and Silber.

Methylgranatanine, obtained by reduction of methylgranatonine, is submitted to exhaustive methylation. Degradation takes place and *cyclooctadiene* is obtained via dimethylaminocyclooctene:



By similar methods it has been possible to convert N-methylgranatanine into *cyclooctatriene* and *cyclooctatetraene*. If its quaternary ammonium base is distilled under ordinary pressure, β -des-dimethylgranatanine is formed, which cannot be exhaustively methylated, because it splits off tetramethylammonium iodide even on careful treatment with methyl iodide. On the other hand, if the quaternary base of N-methylgranatanine is distilled *in vacuo*, the reaction takes a different course. The isomeric α -des-dimethylgranatanine is formed which may be converted into *cyclooctatriene* in the normal way. Finally, *cyclooctatetraene* was obtained from the latter through the dibromide:

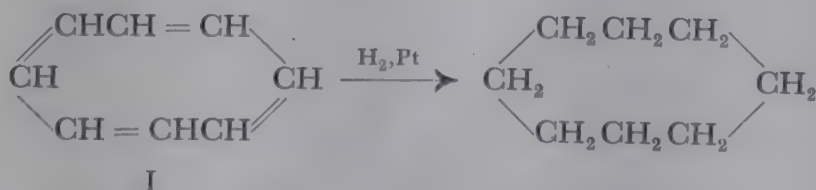




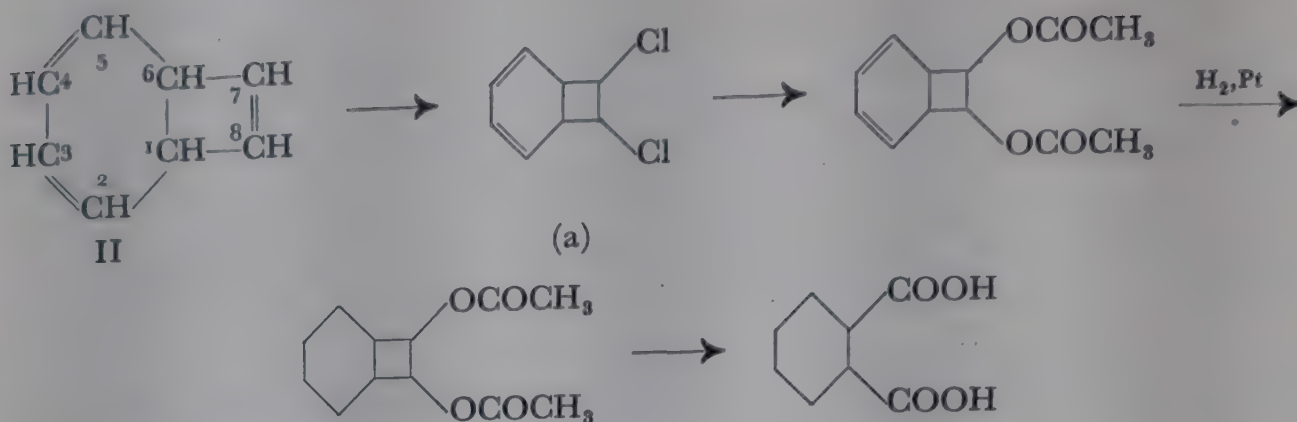
By an elegant synthesis, due to J. W. Reppe, *cyclooctatetraene* has recently become an easily accessible compound. Thus, it is formed in good yield (80%) by polymerization of acetylene, when the latter in tetrahydrofuran solution is heated under pressure, in the presence of inorganic Ni salts (NiCl_2 or $\text{Ni}(\text{CN})_2$) and some ethylene oxide. *Cyclooctatetraene* is a golden-yellow liquid (b.p. $142-143^\circ$ (760mm) and m.p. -7°), which is distinguished by its strongly unsaturated character and high reactivity. It is of particular interest that it can react in three different structural forms:

- 1) as normal *cyclooctatetraene* (I)
- 2) as *bicyclo*-[0:2:4]-octa-2:4:7-triene (II)
- 3) as 1:2:4:5-dimethylene-*cyclohexa*-2:5-diene (III)

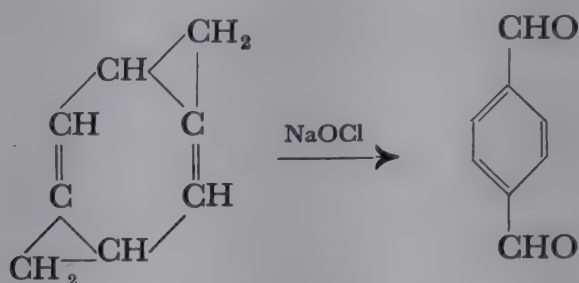
An example of a “normally” proceeding reaction is the hydrogenation of the unsaturated hydrocarbon to give *cyclooctane*:



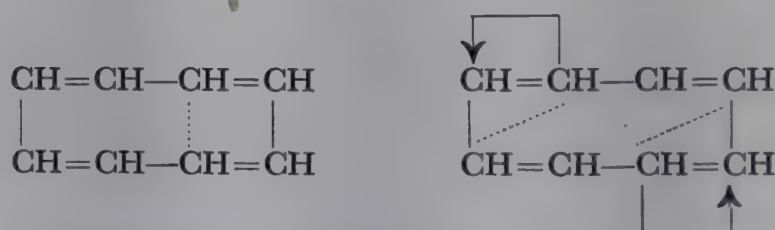
The compound reacts in the *bicyclo*-[0:2:4]-octa-2:4:7-triene form (II) when acted upon by sulphuryl chloride. In this case, the dichloro-derivative (a) is formed, which can be degraded to *cis*-hexahydrophthalic acid in the following way:



Finally, it can react as 1:2:4:5-dimethylene-*cyclohexa*-2:5-diene (III) when oxidized by sodium hypochlorite solution. Terephthalaldehyde is thus obtained (which on further oxidation yields terephthalic acid):



Cyclooctatetraene is thus capable, under the influence of certain reagents, of forming new bridge linkings as indicated by the dotted lines in the following formulæ:



The unsaturated nature of *cyclooctatetraene* shows that Thiele's views on the saturation of the partial valencies of carbon atoms standing between conjugated double bonds, which were used to explain the relatively saturated nature of benzene, do not hold for the *cyclooctane* series.

Cyclooctane, b.p. 150° ; *cyclooctene*, b.p. 145° ; α -*cyclooctadiene*, b.p. 135 – 150° ; β -*cyclooctadiene*, b.p. 143 – 144° ; *cyclooctatriene*, b.p. 147 – 148° ; *cyclooctatetraene*, b.p. 36° (14 mm), 142 – 3° (760 mm).

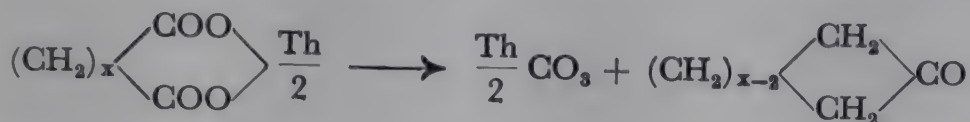
Carbon rings with more than eight carbon atoms. Until the year 1926 practically nothing was known of the existence of carbon rings with more than eight carbon atoms. It had repeatedly been reported that the dry distillation of the calcium salt of sebacic acid gave rise to small amounts of *cyclononanone*, but these products were insufficiently characterized, and were probably not pure.

According to the old strain theory of Baeyer, the existence and stability of higher carbon rings appeared questionable. Assuming a *planar* arrangement of the carbon atoms, the deviation of the carbon valencies from their normal positions amounts to $-9^{\circ} 33'$ for the seven-membered ring, and to $-24^{\circ} 41'$ for the 17-membered ring. The latter thus coincides approximately, in absolute value, with the (positive) distortion of the valency angles of the fairly unstable *cyclopropane*:

3-membered ring deviation	„	+ 24° 44'
4-membered ring	„	+ 9° 44'
7-membered ring	„	— 9° 33'
17-membered ring	„	— 24° 41'

Sachse, Nold, and particularly Mohr, have later shown, however, that in the higher ring systems, the ring members need not necessarily lie in one plane, and that it is possible to conceive of and to construct strain-free models of these systems where the atoms are arranged in more than one plane, thus making probable the existence of stable higher carbon rings.

The investigations of L. Ruzicka have confirmed this prediction. He showed that if the thorium salts of the dicarboxylic acids with eleven or more carbon atoms are dry distilled, cyclic ketones with 10- to 30-membered rings, together with other products can be obtained. The reactions occur according to the general scheme:



Cyclononanone is formed in this way only in traces, but the yields with *cyclo-octanone* and the ketones with more than 9 ring members are somewhat better.

Later K. Ziegler showed that a reaction first discovered in connection with simple nitriles could also serve for the preparation of multi-membered cyclic ketones. The lithium salts of the aliphatic nitriles (see also p. 189) add on to nitriles with formation of imino-nitriles:



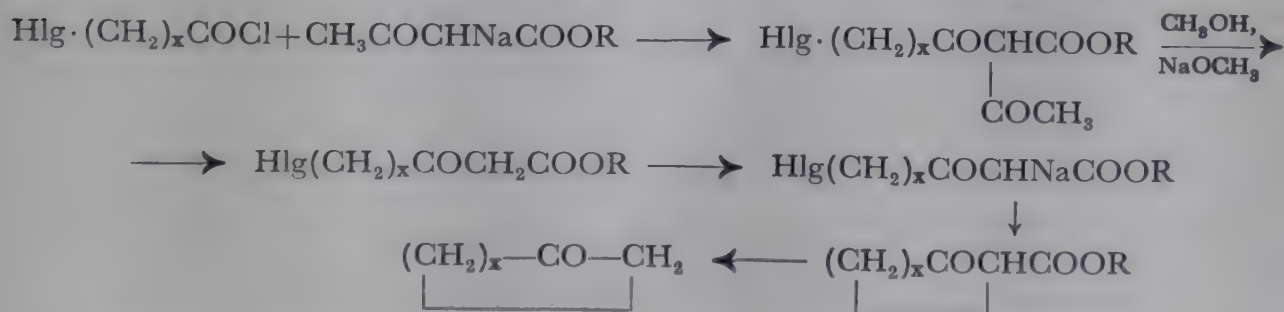
Careful hydrolysis of the latter gives rise to keto-nitriles, and under more energetic conditions, to β -keto-acids. Decomposition of the latter gives ketones.

By the use of this reaction with the nitriles of high-molecular aliphatic dicarboxylic acids, the reaction takes an analogous course, but proceeds intramolecularly. Cyclic keto-nitriles are obtained, and by hydrolysis of the latter, cyclic ketones with large rings are obtained:



If the reactions are carried out in dilute solution, yields of cyclic ketones amounting to more than 50 % of theory can be obtained.

H. Hunsdiecker has developed a further method for the production of cyclic ketones with large rings. He starts from ω -halogeno-acylacetic esters, whose alkali salts, in dilute solution, are converted in 40–75% yield into cyclic ketocarboxylic acids. By splitting off CO_2 from the latter, ketones with large rings are obtained:



The following table gives the boiling and melting points of this cyclic homologous series:

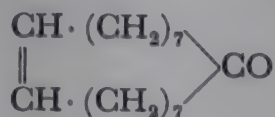
	M.p.	B.p.
<i>Cyclooctanone</i>	40–41°	74° (12 mm)
<i>Cyclononanone</i>	28°	93–95° (12 mm)
<i>Cyclodecanone</i>	28°	100° (12 mm)
<i>Cycloundecanone</i>	9–10° (?)	110° (12 mm)
<i>Cyclododecanone</i>	59°	125° (12 mm)
<i>Cyclotridecanone</i>	32° (?)	138° (12 mm)
<i>Cyclotetradecanone</i>	52°	155° (12 mm)
<i>Cyclopentadecanone</i>	63°	120° (0.3 mm)
<i>Cyclohexadecanone</i>	56°	138° (0.3 mm)
<i>Cycloheptadecanone</i>	63°	145° (0.3 mm)
<i>Cyclooctadecanone</i>	71°	158° (0.3 mm)

All these ketones are, once formed, very stable. If, for example, *cycloheptadecanone* is heated to 400°, a small part of it chars, but the remainder is unchanged. Also no extensive decomposition occurs on heating with hydrochloric acid to high temperatures. The hydrocarbons *cyclopentadecamethylene* and *cycloheptadecamethylene* have been prepared from the ketones with 15 and 17 carbon atoms in the ring, and their behaviour towards hydrogen iodide at high temperatures has been examined. Whilst *cyclopropane* (see p. 645) and *cyclobutane* (see p. 649) undergo rupture of the ring under these conditions, hydrogen iodide has no action on the high-membered cyclic hydrocarbons. The carbon rings with 10 to 30 members are consequently very stable. It may therefore be assumed that their ring carbon atoms do not lie in one plane, but are arranged in space in such a manner that a system results which is more or less free from strain. (Carbon rings with 8–15 carbon atoms in the ring have a refractometric increment of up to -0.6 ; for cyclic ketones with more ring members it is, in some cases, slightly positive. The heats of combustion per CH_2 of the higher cyclic compounds agree with the values found for aliphatic compounds and homologous *cyclopentanes* and *cyclohexanes*, being about 157 kg.-cal.).

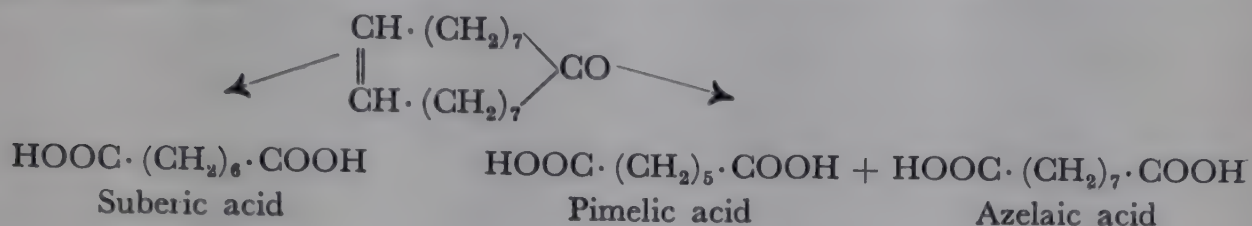
In striking contrast to the great stability of these substances is the difficulty of making them. Here again the Baeyer strain theory cannot explain this paradox, for it regards the ease of ring formation, as well as the stability of the rings, as being a function of the greater or smaller strains within the molecule. Ruzicka, on the other hand, assumes that *two* effects come into the question, which are to be differentiated. One is the *tendency towards ring closure*, which, starting from the most easily formed ethylenic linkage, or “two-membered ring”, decreases as the two newly added carbon atoms between which ring closure is to take place become further apart. Up to rings containing 10 carbon atoms, only the five- and six-membered rings, which are formed remarkably readily, do not obey this rule. In these cases, a second effect would come into play, namely the *preference for forming strainless rings*. If five- and six-membered rings are less strained than those of *cyclopropane* and *cyclobutane*, this can account not only for their great stability, but also for the ease with which they are formed, as regards which, they occupy an exceptional position with respect to all higher and lower ring homologues.

In the synthesis of the higher cyclic ketones the yields actually increase again from the ten-membered ring on, which possibly indicates that the spatial positions of the carbon atoms again become more favourable for ring closure, or that a hindering steric factor, which comes into play particularly in the formation of 8- to 10-membered rings, is removed.

It is surprising to find that higher cyclic ketones also occur in nature. *Civetone*, the most important odoriferous principle of the civet, is an unsaturated cyclic ketone with 17 ring members, having the following formula (Ruzicka):

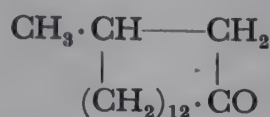


When hydrogenated it gives dihydrocivetone, which is identical with *cycloheptadecanone*. The position of the double bond in civetone was arrived at by oxidation with permanganate, which gave rise to suberic acid, pimelic acid, and azelaic acid:



Civetone was prepared by Hunsdiecker by his method described above. Synthetic civetone has been obtained in two forms (M. Stoll) which are *cis-trans*-isomers (m.p. 31–2° and 29–30°, respectively). Natural civetone is the *cis*-form.

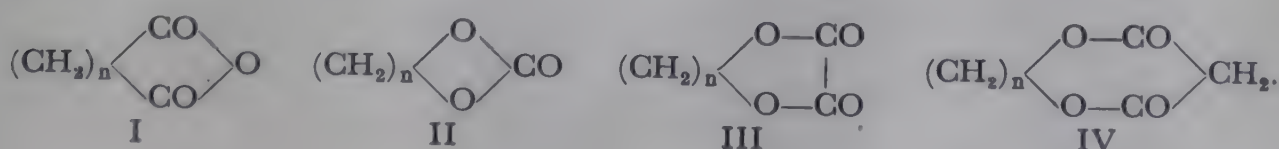
Muscone, the most important perfume of animal musk, is a cyclic ketone with a 15-membered ring; it also can be obtained synthetically:



In the musk glands of the Louisiana musk-rat, *dihydrocivetol*, *cyclopentadecanol* (normuscol or exaltol), *dihydrocivetone*, and *ncrmuscone* have been found (Ph. G. Stevens, Erickson), and in American musk small quantities of *cyclotridecanone* and *cyclononadecanone*.

All the saturated cyclic ketones from *cyclodecanone* to *cyclooctadecanone* have characteristic odours. Ketones with 10- and 12-membered rings smell like camphor, *cyclotridecanone* like cedar, and the smell of ketones with 14–18-membered rings shows the greatest resemblance to that of natural musk, or of its chief constituent *muscone*. The most pronounced is the muscone smell of *cyclopentadecanone*, which has been introduced into perfumery under the name *exaltone*.

The musk-like smell of these substances seems to depend essentially on the cyclic structure and the number of members in the ring, whilst the nature of the atoms of the ring can be varied without producing any essential alteration in the fundamental perfume. It has already been mentioned (p. 265) that 15–17-membered lactones are characterized by a musk-like smell, and this is also the case, according to the researches of Hill and Carothers, for cyclic anhydrides and esters of the types I–IV, if the rings are made up of 15–16 atoms:



PART III.
HETEROCYCLIC COMPOUNDS

Section I.

Simpler Heterocyclic Compounds with a more or less Aromatic Nature

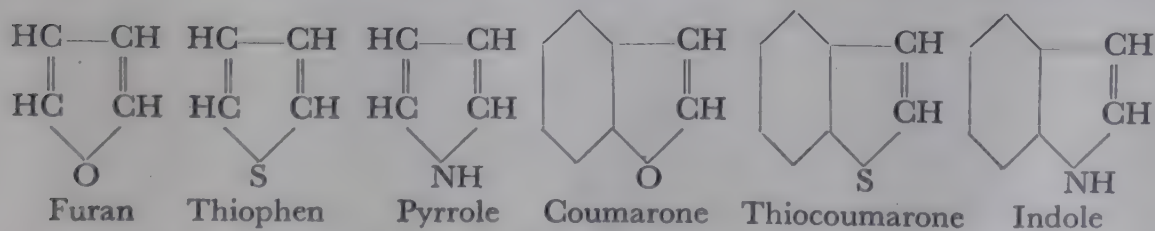
In a short exposition of Organic Chemistry, which, like the present, is intended for teaching purposes, it is not always possible or advisable to draw sharp boundaries between the various sections. Internal relationships in isolated groups of compounds make it appear convenient to deal with them outside the rigid framework of a systematic treatment. Others have to be classed apart for didactic reasons. Thus, in this section dealing with "*heterocyclic compounds*" it is not by any means all those substances which have cyclic nuclei containing different kinds of atoms, that are considered.

The large groups of azine, oxazine, and thiazine dyes, etc. have been dealt with in connection with the quinone dyes in the section on "*Aromatic Chemistry*". In the same part the coumarin and pyrone compounds, including the flavone, flavanol, and pyrylium dyes, and also indigo and its analogues, have been considered, partly in connection with the aromatic hydroxy- and amino-acids. When dealing with the aliphatic amino-acids, several other protein amino-acids with a heterocyclic nature were encountered, and in connection with the hydroxy-acids and amino-acids, the heterocyclic lactones and lactams were dealt with. It appears important for the student to obtain an elementary knowledge of these classes of substances long before he makes himself familiar with the properties and peculiarities of special heterocyclic ring-systems or proceeds to the study of the plant bases (alkaloids).

Part III of this book really comprises, therefore, only some of the heterocyclic systems. Its second section is devoted to the alkaloids. In the first section it is essentially those *simpler five- and six-membered heterocyclic rings*¹ which are more or less "aromatic" in nature (i.e. they recall in their reactions benzene and its derivatives) that are considered. These compounds are derived from the following bodies:

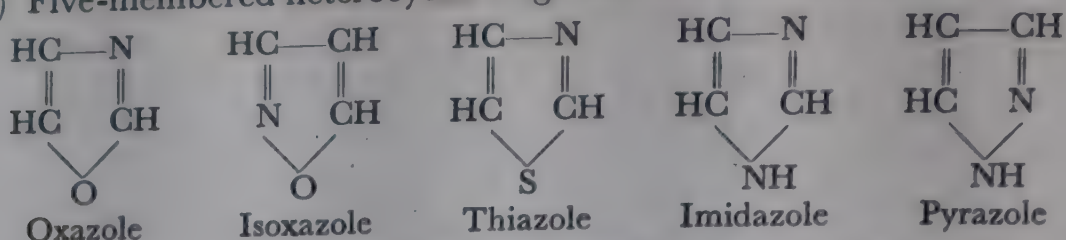
A. FIVE-MEMBERED HETEROCYCLIC RINGS

(a) Five-membered heterocyclic rings with *one* atom different from carbon:

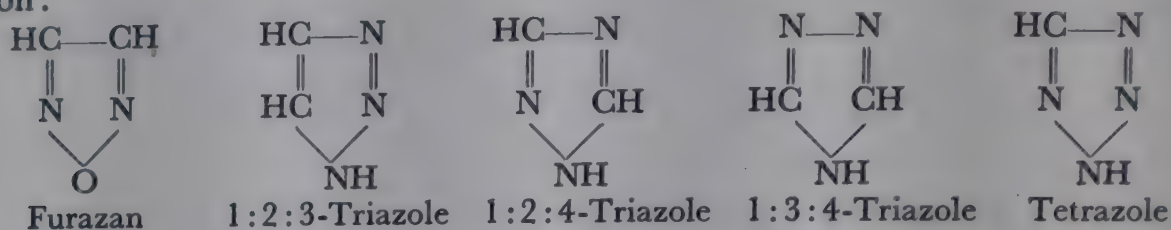


¹ Compare, for example, V. MEYER and P. JACOBSON, *Lehrbuch der organischen Chemie*, II Bd. 3. Teil, Leipzig, (1920).

(b) Five-membered heterocyclic rings with *two* atoms different from carbon :

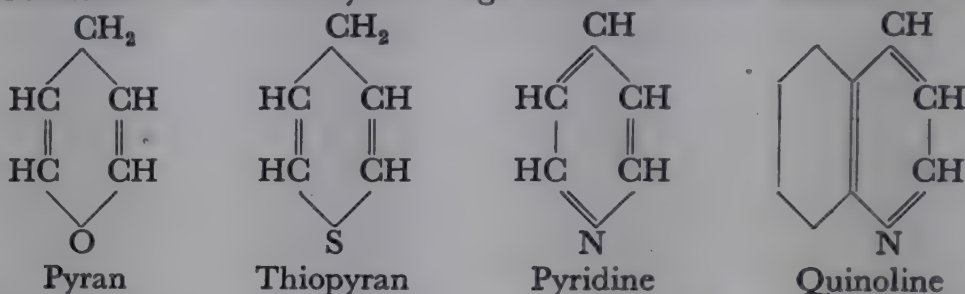


(c) Five-membered heterocyclic rings with *three or more* atoms different from carbon :

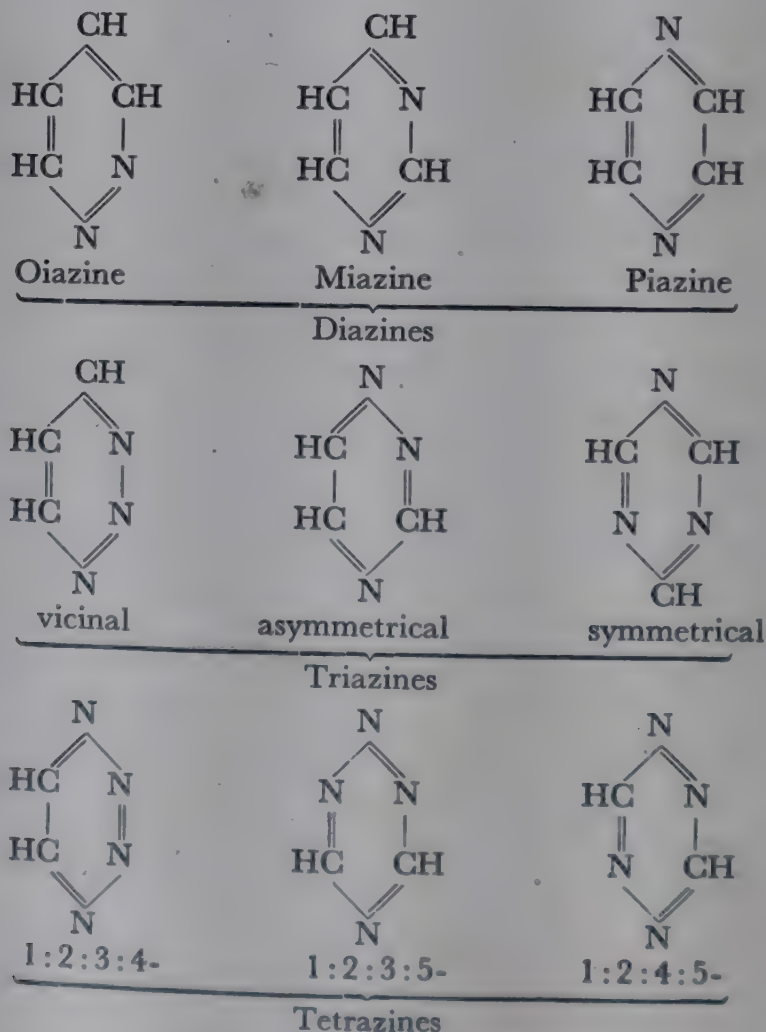


B. SIX-MEMBERED HETEROCYCLIC RINGS

(a) Six-membered heterocyclic rings with *one* atom different from carbon :



(b) Six-membered heterocyclic rings with *more than one* atom different from carbon :

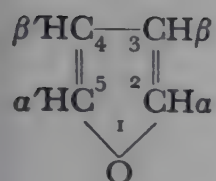


Whilst it is only recently that carbocyclic compounds with more than nine carbon atoms have been proved to be capable of existence and to be stable (see p. 749), heterocyclic rings with 12 and 14 members have been known much longer. Also in these cases there is no doubt that the rings are not planar in structure; the components must be arranged in several planes.

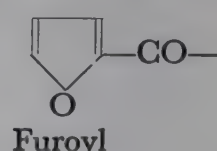
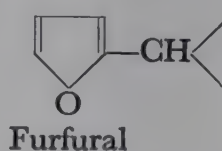
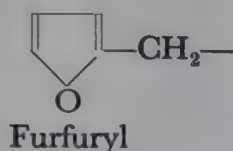
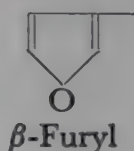
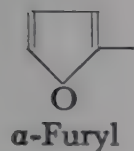
The numbering of the heterocyclic ring systems is carried out as follows: Where there is only one hetero-atom it is numbered 1. If more than one hetero-atom is present, one of them is numbered 1, and the others with the lowest possible numbers, O taking precedence to S, and S to N.

CHAPTER 59. FIVE-MEMBERED HETEROCYCLIC RINGS WITH ONE HETERO-ATOM

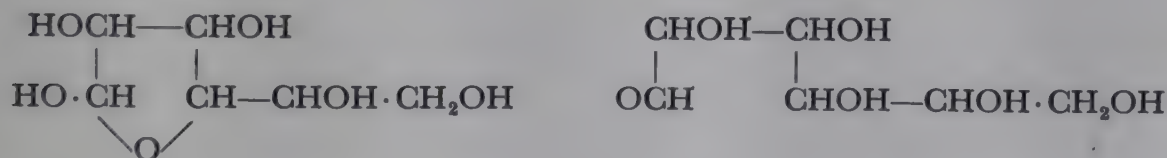
Furan group



FURAN, whose carbon atoms are numbered as shown, gets its name from *furfural*, the furanaldehyde, which can be prepared in large quantities from bran ("furfur"). The radical which has one hydrogen atom less than furan is called *furyl*. The names "furfuryl", "furfural", and "furoyl" ("furfuroyl") radical are also used:

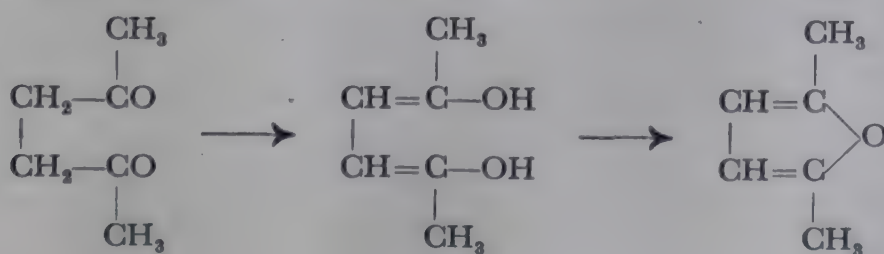


There is a close connection between furan derivatives and aliphatic compounds. In particular cases, as with the sugars, tautomerism can even occur, a sugar being able (as has been mentioned on p. 323) to react in the open-chain aldehydic form, or in the oxide form, e.g. as a furan derivative:



The most important method for making furan compounds consists in the *elimination of water from 1:4-diketones* or 1:4-dihydroxy-compounds. Zinc chloride, concentrated acids, etc. are suitable for bringing about the dehydration.

Thus acetonylacetone is converted into α,α' -dimethylfuran, the dienolic form of the ketone being probably produced intermediately:

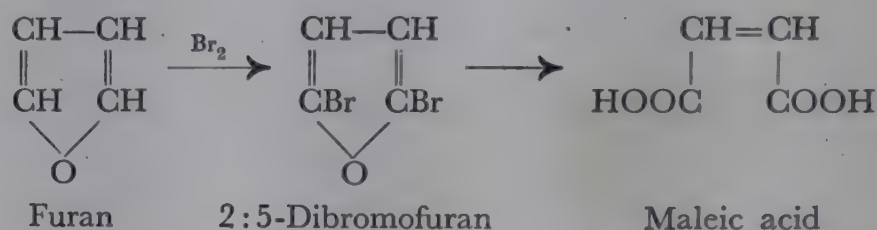


Pentoses break down under the dehydrating action of concentrated acids into furfural (p. 330–31).

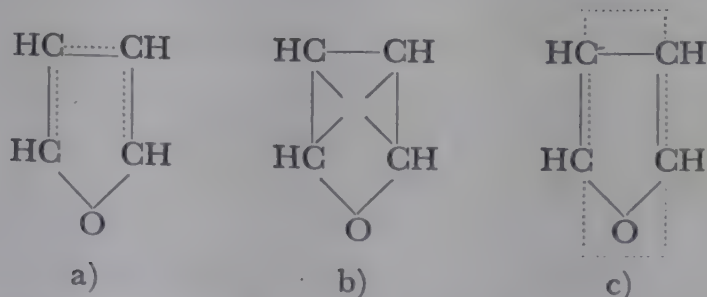
The best method of making furan itself is the elimination of carbon dioxide from furan- α -carboxylic acid (pyromucic acid, see p. 760) or from furan- α,α' -dicarboxylic acid (dehydromucic acid, see p. 760). The decomposition is conveniently carried out in a basic medium (e.g. crude tar bases) in the presence of copper sulphate or copper as a catalyst (170°–220°).

Furan is a water-clear liquid with an odour resembling that of chloroform. It boils at quite a low temperature (31–32°). It is hardly attacked at all by alkalis, but deep-seated decomposition occurs with acids. In spite of the presence of two double bonds, furan is fairly difficult to reduce. Sodium amalgam has no effect. With hydrogen and nickel, osmium, or palladium oxide, hydrogenation occurs to furan tetrahydride, but for this high temperatures are also necessary.

This behaviour on the part of furan already recalls that of benzene, but it also resembles the aromatic hydrocarbon, in that halogens do not add on to it to give stable addition products, but substitution occurs, e.g. with bromine. The substitution takes place at the two α -carbon atoms, since dibromofuran gives maleic acid on oxidation:



The aromatic character of furan, which is shared to the same degree by pyrrole, thiophen, and pyridine, etc. brings forward the same unsolved problems as in the case of benzene (see p. 378). Similar views as were put forward in connection with the chemistry of benzene have been transferred to the heterocyclic series: the “oscillating linkage” (a), the “centric formula” (b), Thiele’s neutralization of valencies in a conjugated system of double bonds (c) have been put forward

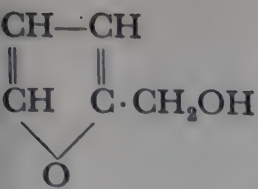


without being essentially nearer to the solution of the problem.

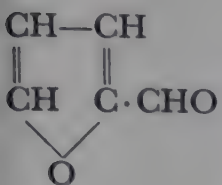
Furan gives an intense green coloration to a pine splint dipped in hydrochloric acid, and this is used for the detection of the substance.

If furan is mixed with ammonia and passed over Al_2O_3 at 450°, pyrrole (see p. 768) is formed. If the ammonia is replaced by hydrogen sulphide, thiophen (see p. 764) is produced.

α -Methylfuran, or *silvan*, is found in so-called wood oil, e.g. in beech-tar oil. It boils at 63°. It gives a green coloration to a pine splint dipped in hydrochloric acid. It also exists in a labile form (methylene-dihydrofuran?).



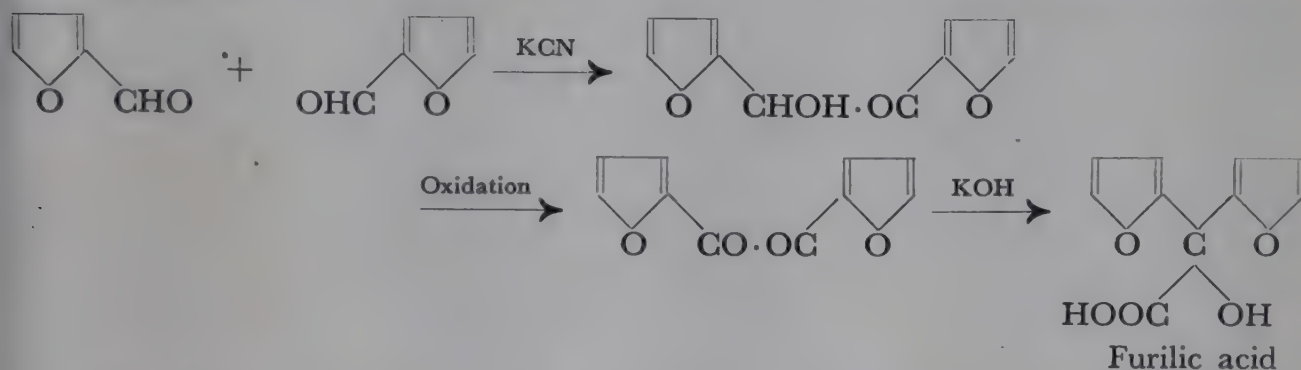
α -FURFURYL ALCOHOL is easily obtained by the reduction of the corresponding aldehyde, furfural (see below). The compound has also been found in clove oil, and in the extract of roasted coffee. It boils at 170–171°. It is a liquid with a faint odour.



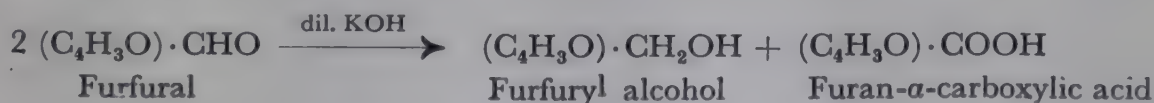
α -FURALDEHYDE, FURFURALDEHYDE, FURFURAL, is amongst the easiest obtainable furan derivatives. It is usually prepared by heating bran with dilute sulphuric acid (Stenhouse). The pentoses, which, as pentosans, form a considerable proportion of bran, lose water in the manner mentioned above, and are converted into furfural. Also the small quantities of furfural which have been detected in fusel oil, essential oils, and in other places have probably been produced from carbohydrates.

The aldehyde is a colourless liquid, boiling at 162°, which easily turns brown. It gives a red coloration with aniline acetate. Phloroglucinol condenses with it to give a green-black insoluble compound, which serves for the quantitative estimation of the aldehyde, and also of pentoses (Tollens) (see p. 331).

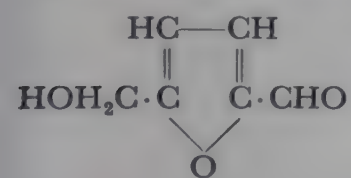
In its chemical properties furfural shows great similarity to benzaldehyde. Like the latter, furfural undergoes a "benzoin condensation" in the presence of cyanide ions. A substance called *furoin* is thus produced, which is converted into *furil* on oxidation (analogy with the synthesis of benzil). *Furil* rearranges by boiling with caustic potash into *furilic acid*, a compound corresponding to benzoic acid:



The disproportionation of aldehyde into an alcohol and an acid (Cannizzaro's reaction) which occurs with great readiness with the aromatic aldehydes, is also observed with furfural:



Furfural can be oxidized to furan- α -carboxylic acid (*pyromucic acid*) also by means of silver oxide.



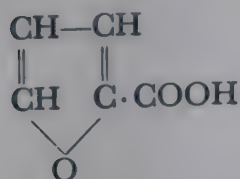
ω -HYDROXYMETHYL-FURFURAL. Just as furfural is produced from pentoses, ω -hydroxymethyl-furfural is obtained from hexoses by the action of acids, ketoses (fructose, sorbose) being better suited than aldohexoses for this reaction. Oxalic acid, for example, has proved useful for the

purpose. For the presumed course of the degradation of ω -hydroxymethyl-furfural to lævulinic acid, see p. 271–72.

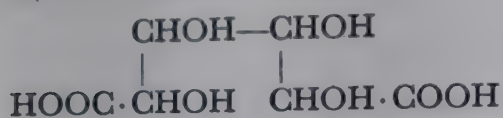
This derivative of furfural also gives some beautiful and sensitive colour reactions. Thus, with resorcinol and hydrochloric acid it gives a red precipitate,

which is used in the detection of hexoses (Seliwanow's reaction), and with β -naphthol and concentrated sulphuric acid it gives a dark blue colour, etc.

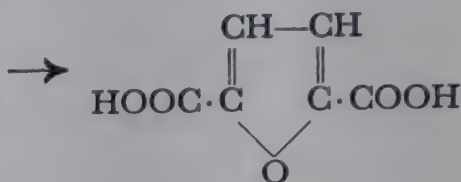
ω -Hydroxymethyl-furfural is a crystalline substance, melting at 33° , and forming colourless needles. It is almost odourless, and is very hygroscopic, deliquescent rapidly when allowed to stand in air, and mixing with water in all proportions. Its boiling point is about 120° (0.2 mm).



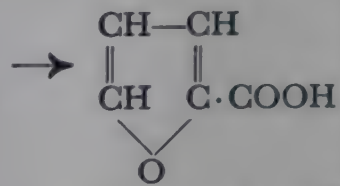
ation of carbon dioxide:



Mucic acid



Dehydromucic acid



Pyromucic acid

The oxidation of furfural (see p. 759), however, is mostly used for the preparation of pyromucic acid.

In general chemical behaviour there are some similarities between pyromucic acid and benzoic acid. By the action of bromine furan- α -carboxylic acid gives a monobromo-derivative (5-bromofuran-2-carboxylic acid), with nitric acid it gives a nitro-compound, and with sulphuric acid a sulphonic acid. Hydrogen and palladium reduce it to tetrahydropyromucic acid. On the other hand, there are considerable differences in the stability of the derivative of benzene and that of furan. The latter undergoes ring rupture fairly easily. For example, sodium hypobromite will convert pyromucic acid to aldehydomaleic acid.

The melting point of pyromucic acid is 133° (corr.). It is not very soluble in water, and gives a strongly acid reaction. Its dissociation constant is considerably greater than that of benzoic acid.

5-FORMYLPYROMUCIC ACID (m.p. 202°) is produced by the isomerization and anhydridization of 5-ketogluconic acid on heating with methyl alcoholic hydrochloric acid (Votoček):

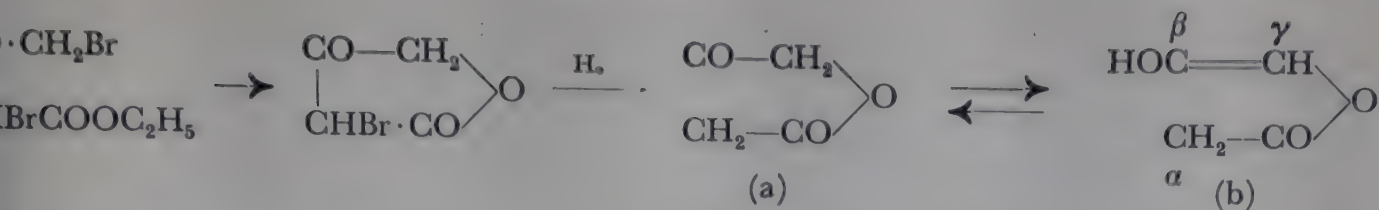


DEHYDROMUCIC ACID (furan- α, α' -dicarboxylic acid) is obtainable from mucic acid or saccharic acid in several ways. To prepare the substance these dicarboxylic acids are heated with concentrated sulphuric acid or hydrobromic acid.

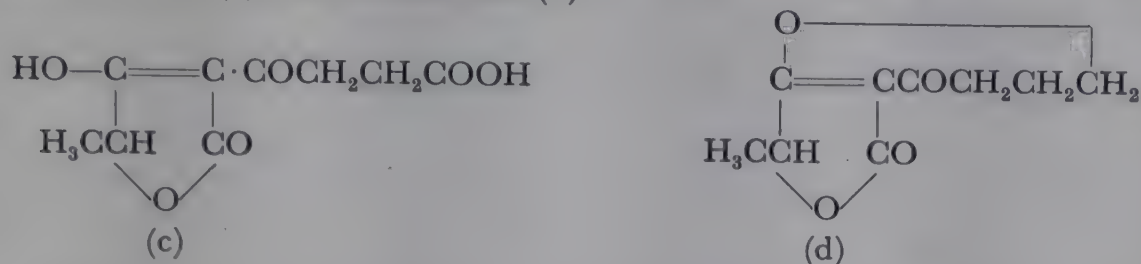
Dehydromucic acid is only slightly soluble in water. It crystallizes well, and on careful heating sublimes. When rapidly distilled, however, it breaks down into carbon dioxide and pyromucic acid.

Amongst its chemical reactions, its behaviour towards reducing agents must be specially mentioned. It is reduced more easily than pyromucic acid to the tetrahydro-derivative. This corresponds with the benzene series, where dicarboxylic acids are likewise more easily hydrogenated than benzoic acid.

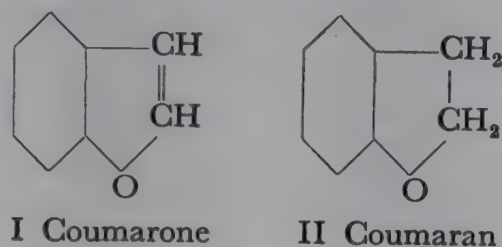
TETRONIC ACID (a) can be regarded formally as a diketo-derivative of tetrahydrofuran: it exists, however, as the enol form (b). It is accessible in a number of ways, e.g. from α, γ -dibromoacetoacetic ester which, on heating, is converted into α -bromotetronic acid. Reduction of the latter yields tetronic acid:



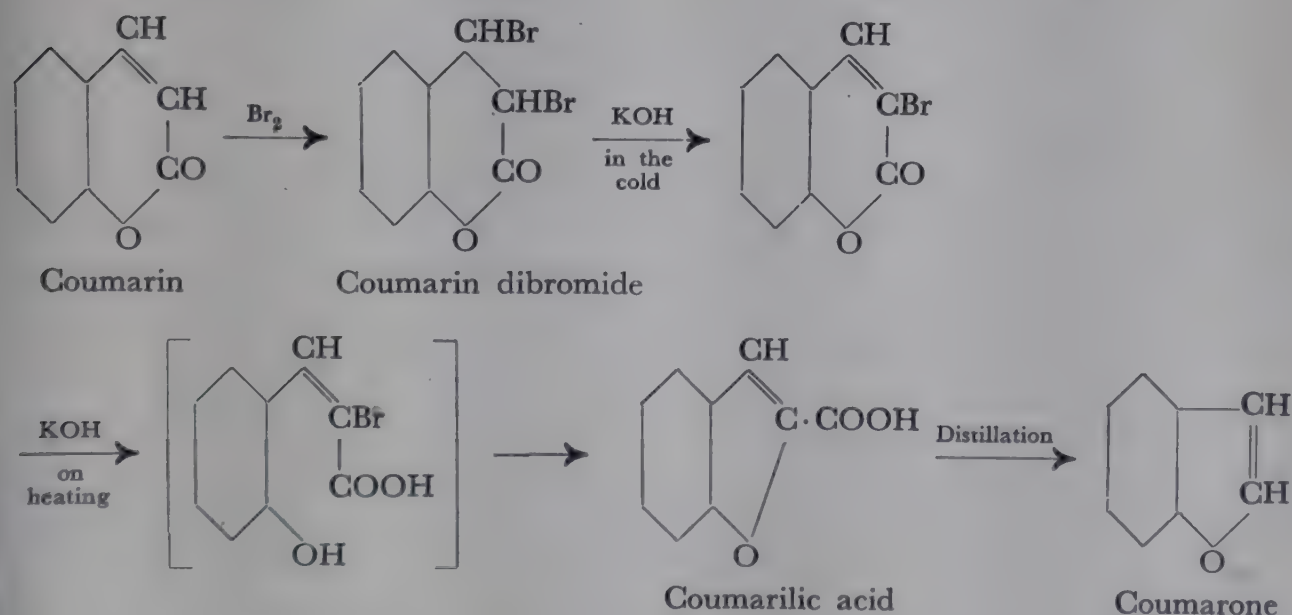
This acid is the parent compound of numerous naturally occurring substances, in particular, of metabolic products from moulds. Some examples are *l*- γ -methyltetronic acid, carolinic acid (c), and carolic acid (d):



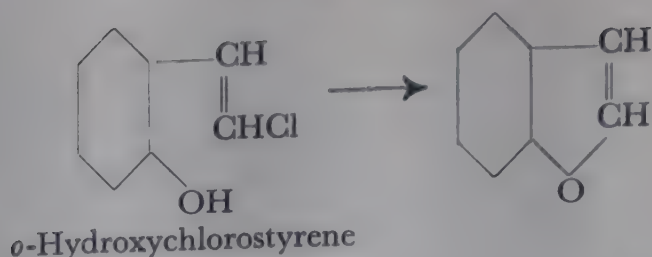
Coumarone. Coumarone is a substance in which the furan ring is condensed with a benzene nucleus in the ortho-position, as shown in formula I. Coumarone hydrogenated in the furan part is usually called *coumaran* (II)



Of the numerous known *syntheses of coumarone*, only two can be mentioned here. The first starts with coumarin (see p. 538). Coumarin dibromide, obtained from it by the addition of bromine, is treated with alkali, which converts it into bromocoumarin, and this, on heating is converted into *coumarilic acid*. On distillation, the latter breaks down into carbon dioxide and coumarone:



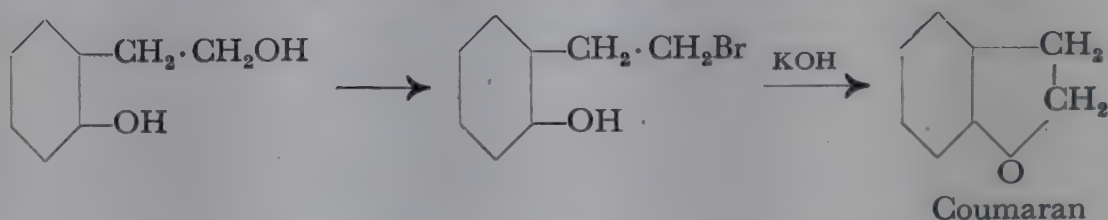
A second method of preparing coumarone depends on the splitting off of hydrogen chloride from *o*-hydroxychlorostyrene by means of alkali:



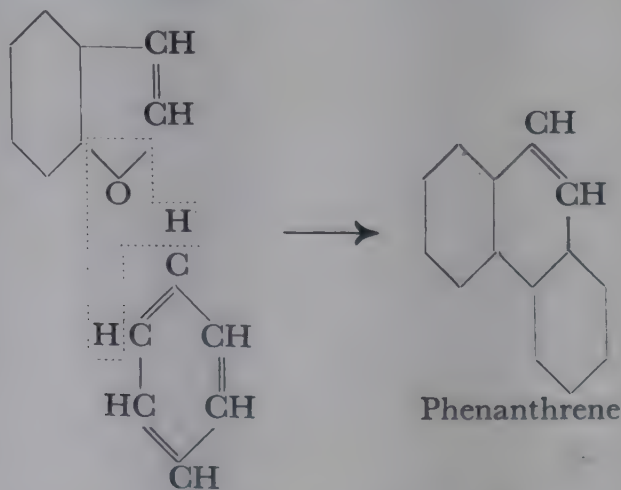
Also, if coumarin is passed through a tinned iron tube at 860° , coumarone is formed in good yield.

Coumarone is found, together with various higher homologues, in coal-tar, distilling over particularly in the fraction boiling between 168° and 175° . It is a colourless oil, b.p. $173-175^{\circ}$. It is fairly stable towards alkalis and ammonia, but, on the other hand, it is readily attacked by potassium permanganate, adds on bromine, and readily resinifies under the action of sulphuric acid. This "*coumarone resin*" has recently become a technical product. It is prepared from coal-tar fractions which are rich in coumarone and its homologues. It consists of various polymers of coumarone, and on distillation gives back about 20% of monomolecular coumarone.

The reduction of coumarone is fairly readily carried out. The product, *coumaran*, can also be obtained by other methods, e.g. ring closure of β -(*o*-hydroxyphenyl)-ethanol, which is best accomplished through the bromide:



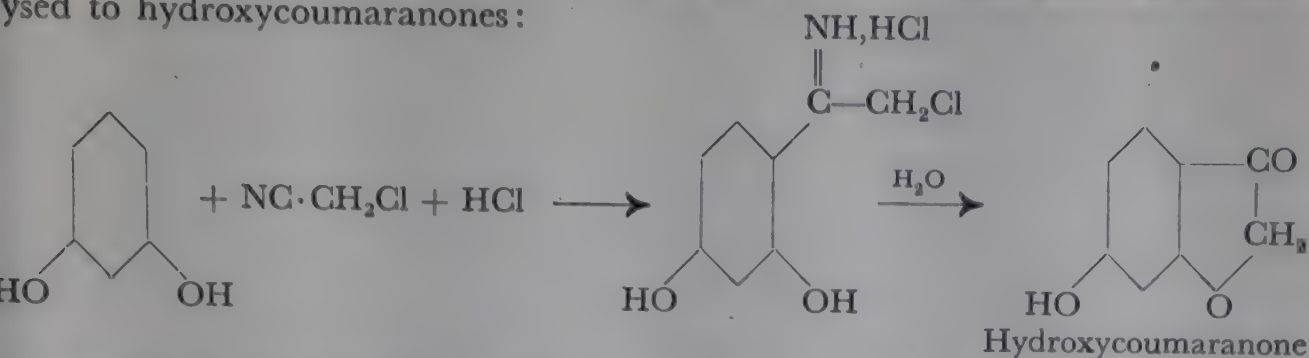
The fact that coumarone will condense with various aromatic hydrocarbons at high temperatures to give polynuclear hydrocarbons, is of great interest. If it is passed with benzene through a red-hot tube, *phenanthrene* is formed. If naphthalene is used instead of benzene, *chrysene* is formed:



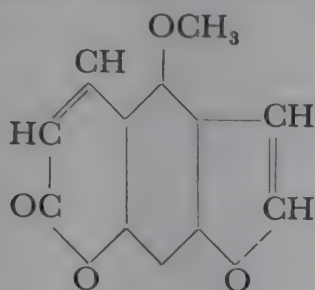
Since coumarone occurs in tar, a not inconsiderable fraction of the multi-nuclear hydrocarbons present in coal-tar may owe their origin to such condensation processes.

Hydroxy-ketones of the coumarone series, *hydroxycoumaranones*, can be easily prepared by a simple synthesis. If an ethereal solution of chloroacetonitrile and resorcinol or phloroglucinol is treated with hydrogen chloride, the hydrochlorides

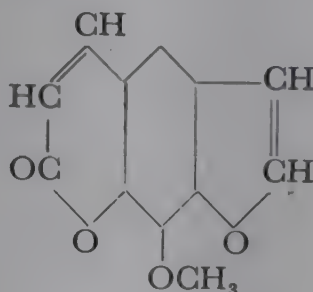
of ketimines are produced, which on boiling with water or weak alkalis are hydrolysed to hydroxycoumaranones:



Coumarone derivatives are often met with in nature. Thus, *bergapten* from the fruit-cases of *Citrus bergamia*, and *xanthotoxin*, which is found together with bergapten in *Fagara xanthoxyloides*, have been formulated as follows by Thoms:

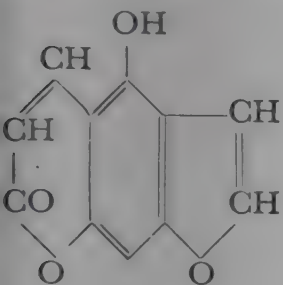


Bergapten

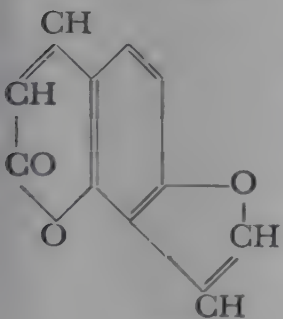


Xanthotoxin

They are therefore to be regarded as methoxylated furano-coumarins. Both are very toxic towards fish.

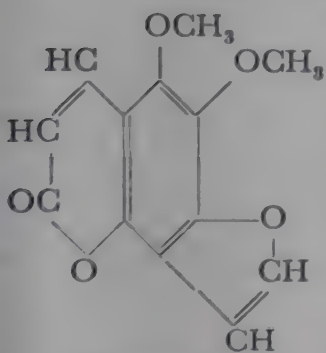


The parent substance of bergapten is *bergaptol*, which is contained in oil of bergamot. M.p. 280–282°.

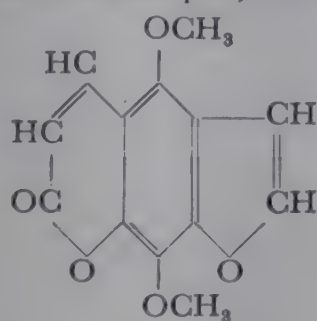


The linkage of furan with the coumarin ring can also take place in another way. Thus, for example, *angelicin*, a constituent of the root-oil of *Angelica archangelica* L. has the accompanying formula.

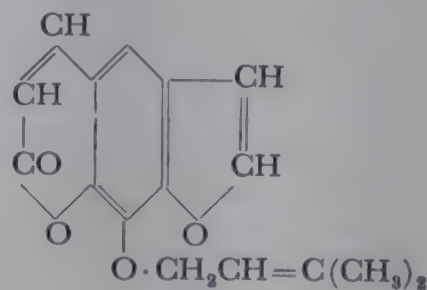
Vegetable fish-poisons of a furano-coumarin nature occur very widely in plants. Investigations carried out in recent years, especially by E. Späth, have led to the discovery of a large number of such compounds. As examples, the following may be mentioned:



Pimpinellin
from the root of
Pimpinella saxifraga

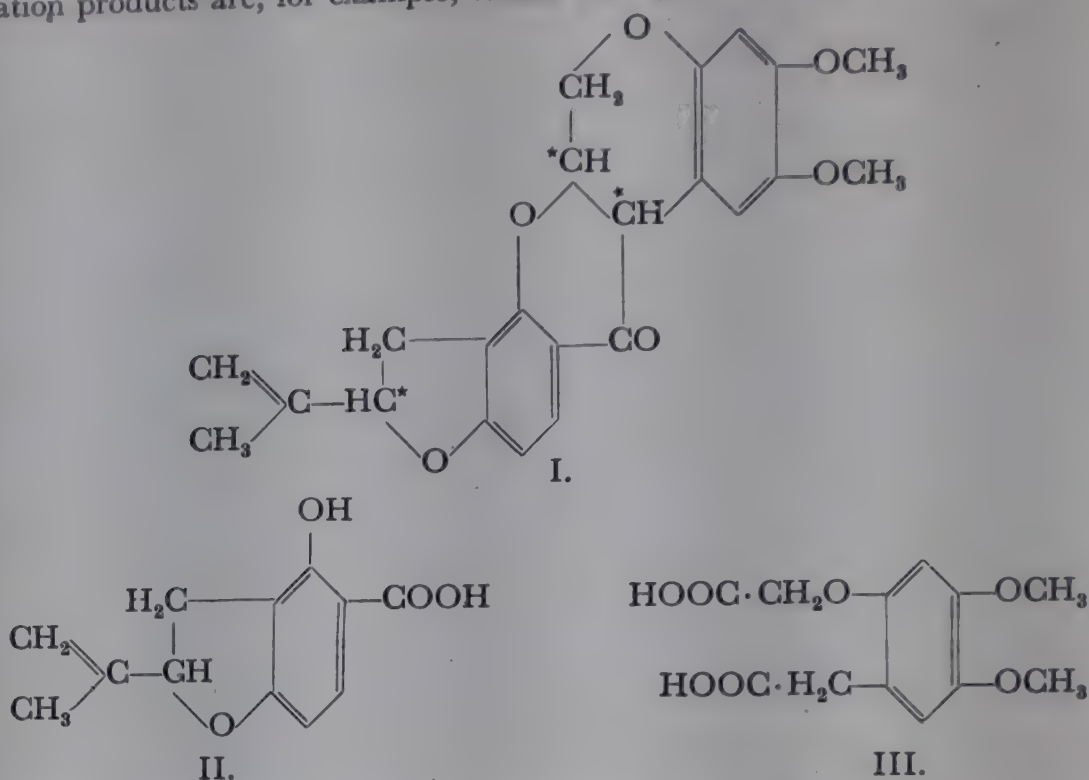


IsoPimpinellin
from *Pimpinella*
saxifraga

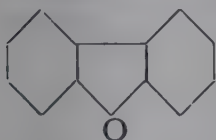


Imperatorin from
masterwort
(*Imperatoria ostruthium*).

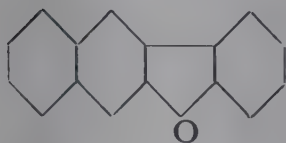
The most important poison of the derris root, which is much used as an insecticide¹, is *rotenone*. It has, according to La Forge and Butenandt, formula I. Amongst its numerous degradation products are, for example, tubaic acid (II) and derric acid (III):



Systems in which the furan ring is condensed with more than one benzene nucleus are known in large numbers. Only a few of them can be mentioned here:



Biphenylene oxide is obtained in various ways, and fairly easily by distillation of phenol or diphenyl ether with lead oxide. The compound crystallizes in colourless leaflets; m.p. 87°, b.p. 287—288°.

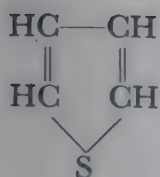


Brazan is a degradation product of *brazilin*, the dye of logwood (see p. 560); m.p. 202°. Also this compound has been synthesized.



Morphenol, which will be studied later as an important degradation product of the opium alkaloid morphine, also contains in its molecule a furan ring surrounded by benzene nuclei. It melts at 145°. Morphenol can be broken down by means of sodium to 3:4-dihydroxyphenanthrene (morphol).

Thiophen group²



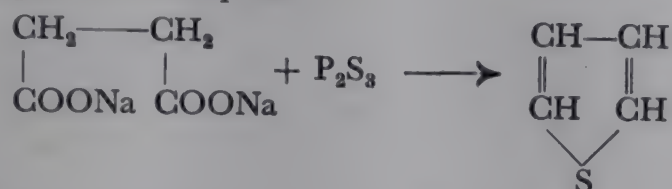
Thiophen, a constant impurity in crude benzene and the cause of the indophenin reaction (see p. 385), is very similar to benzene in its physical and chemical properties, in spite of its completely different composition, and is not easy to separate from the aromatic hydrocarbon. Fractional distillation cannot be used — the boiling points of the two compounds are too close. Benzene boils at 80.4°, and thiophen at 84°.

¹ DONALD E. H. FREAR, *Chemistry of Insecticides and Fungicides*, New York and London, (1943).

² V. MEYER, *Die Thiophengruppe*, (1888). — W. STEINKOPF, *Die Chemie des Thiophens*, Dresden and Leipzig, (1941).

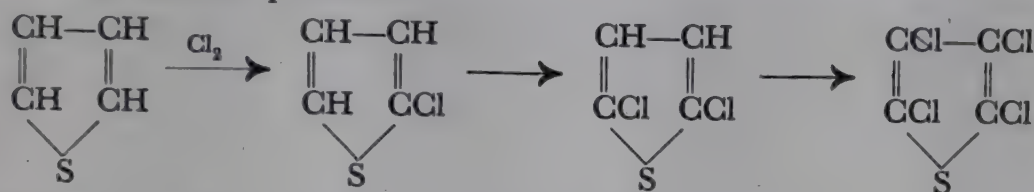
A method of isolating thiophen from benzene is based on the fact that it is more readily sulphonated than benzene. If, therefore, the mixture is shaken with a little concentrated sulphuric acid, thiophensulphonic acid is chiefly formed, which dissolves in the sulphuric acid layer. A second method of separating it depends on the easy mercuration of thiophen. On treatment of the crude benzene with mercury acetate, only the sulphur compound is mercurated, the reaction product separates out and can readily be decomposed again into its components by heating with hydrochloric acid.

Thiophen may be obtained synthetically either by distillation of sodium succinate with phosphorus trisulphide:



or by passing acetylene over heated pyrites. The latter reaction gives in addition to large quantities of thiophen (up to 50%), some of the homologues of the compound.

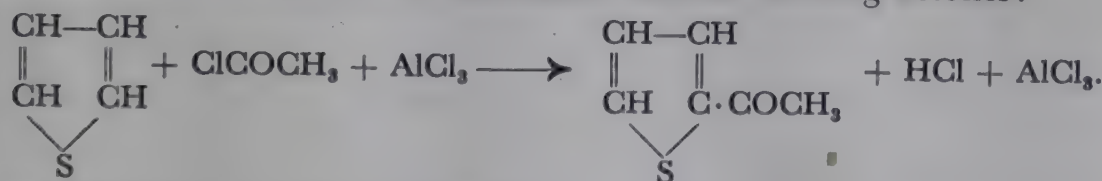
The "aromatic" character of thiophen is even more strongly marked than that of furan. *Chlorination* of the compound leads successively to mono-, di-, and tetrachloro-substitution products:



Under other conditions, however, *addition* of chlorine to thiophen can also take place, as in the case of benzene, with formation of 2:3:4:5-tetrachloro-, 2:2:3:4:5-pentachloro-, and 2:2:3:4:5:5-hexachlorotetrahydrothiophen.

It is difficult to *nitrate* thiophen. This is best done by passing thiophen vapour into fuming nitric acid. The nitro-group enters in the α -position. The well-crystallized α -nitrothiophen (m.p. 46°; b.p. 224–225°) can be reduced to the amino-compound, an exceedingly unstable substance which cannot be diazotized, but which couples with diazonium salts like aromatic amines.

By *sulphonation*, thiophen is converted into the α -sulphonic acid. It reacts violently with *acid chlorides* and aluminium chloride forming ketones:



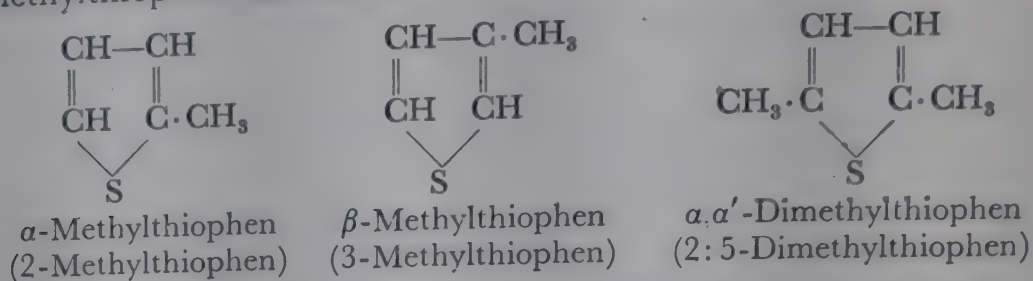
Such acylations are also very effectively carried out by using other catalysts, e.g. ZnCl_2 , I_2 , HI , etc.

Thiophen is remarkably stable towards reducing agents, and towards potassium permanganate.

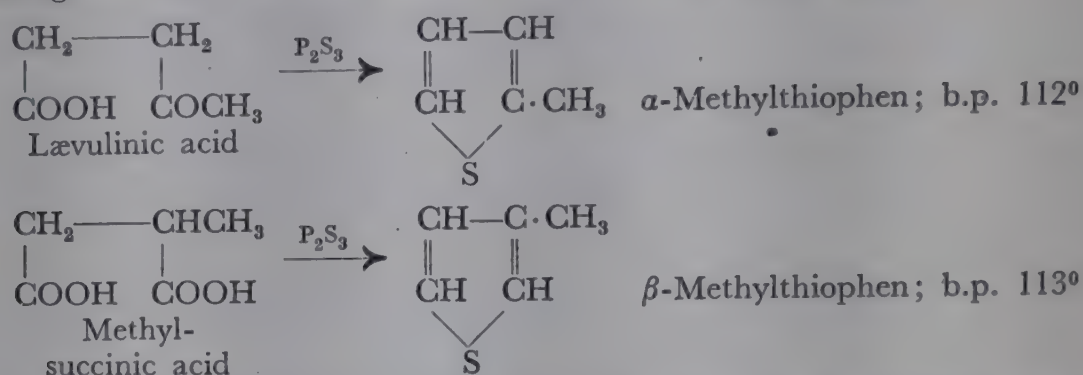
The whole behaviour of this sulphur compound thus recalls to the highest degree that of benzene. Thiophen is a colourless, mobile liquid, immiscible with water, which can be frozen to a crystalline solid at low temperatures. Our more accurate knowledge of thiophen is due chiefly to V. Meyer and his co-workers, who also contributed most to the development of the whole thiophen group.

The selenium analogue of thiophen, *selenophen*, has been obtained from acetylene and selenium at 400°. The substance is stable, and reacts slowly like thiophen. It boils at 110°; m.p. —38° (Briscoe and Peel).

Homologues of thiophen are likewise contained in coal-tar and are found in the toluene and xylene fractions; α - and β -methylthiophen (*thiotolens*) and α,α' -dimethylthiophen have been detected in the same source:



Distillation of lævulinic acid or methylsuccinic acid with phosphorus trisulphide gives rise to the two thiotolens (monomethylthiophens):

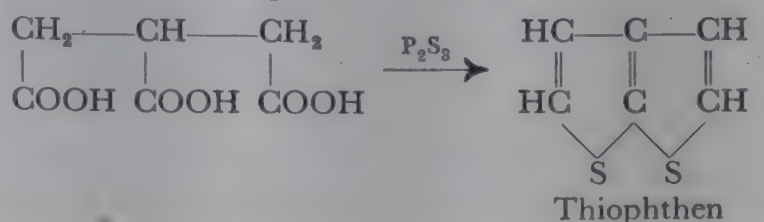


In physico-chemical behaviour the methylthiophens resemble on the one hand toluene, with which they have, for example, almost identical boiling points, and on the other thiophen, entering into very similar reactions to that substance.

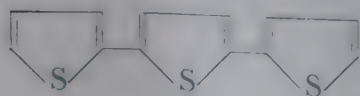
The four possible dimethylthiophens are also known. They are sometimes known as *thioxens*.

2:3-Dimethylthiophen, b.p. 136–137°; 2:4-dimethylthiophen, b.p. 137–138°; 2:5-dimethylthiophen, b.p. 134°; 3:4-dimethylthiophen, b.p. 144–146°.

The molecule of *thiophthen* consists of two thiophen nuclei fused in the *ortho*-positions. The compound can be obtained by distillation of citric acid or tricarballylic acid with phosphorus trisulphide:



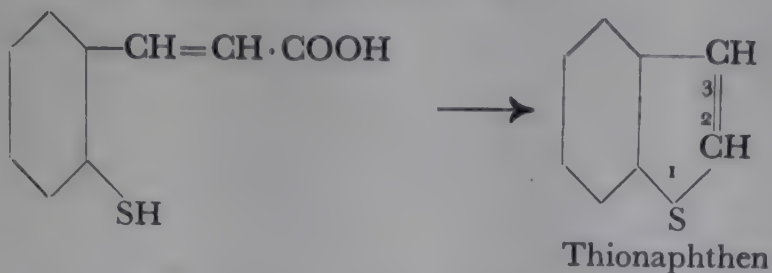
Its behaviour towards picric acid is noteworthy. It forms a difficultly soluble picrate, thus resembling naphthalene. Also its boiling point (226°) is not widely different from that of naphthalene (218°).



A substance consisting of three thiophen units linked together is α -terthienyl, which has been found in the petals of *Tagetes erecta* L. (Zechmeister).

Thionaphthen. Thionaphthen is the sulphur compound corresponding to coumarone, and thus consists of a benzene nucleus with a thiophen nucleus condensed in the *ortho*-position.

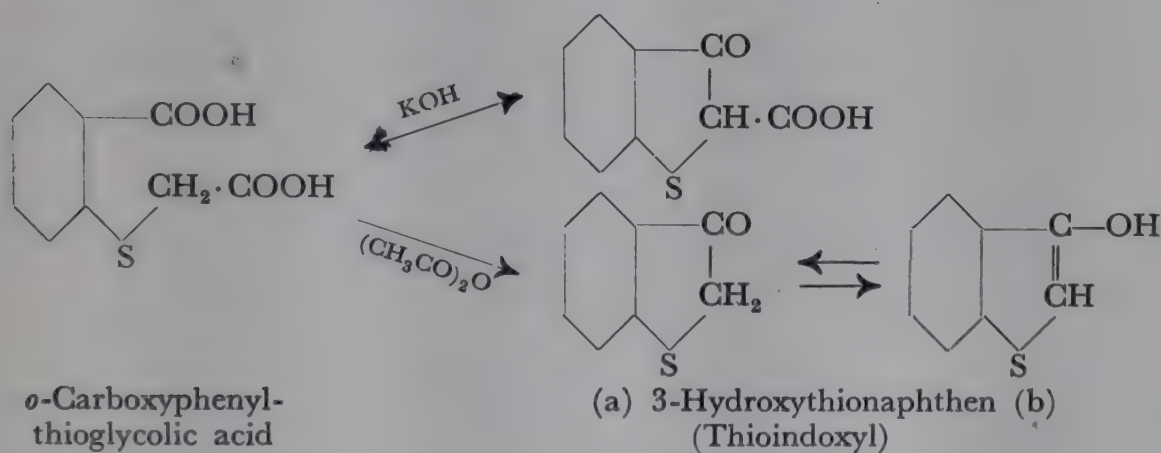
The best synthetic method for preparing it consists in the oxidation of *o*-mercaptocinnamic acid with potassium ferricyanide:



Thionaphthen smells like naphthalene, and boils at almost the same temperature as the latter (221°). It melts at 32°.

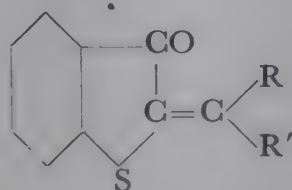
Although not itself of practical importance, thionaphthen is the parent substance of the technically important *3*-hydroxythionaphthen, and the *thioindigo dyes*, of which the first and best-known member is Thioindigo red B. The thioindigo dyes have already been dealt with in this book on pp. 574 ff. Some supplementary remarks on the methods of preparation and the properties of 3-hydroxythionaphthen only will be given here.

The most suitable method of preparation depends on the elimination of water from *o*-carboxyphenylthioglycolic acid, which gives hydroxythionaphthen-carboxylic acid when caustic potash is used as condensing agent, and 3-hydroxythionaphthen directly when acetic anhydride is used. Hydroxythionaphthen-carboxylic acid is very unstable in the free state, and loses one molecule of carbon dioxide even on boiling with water:



Two tautomeric formulæ, (a) and (b), can be written for 3-hydroxythionaphthen. Derivatives of both forms are known.

The compound is colourless, melts at 71°, and smells like naphthol. Like the naphthols it couples readily with diazonium salts, and condenses with reactive carbonyl compounds, aldehydes and ketones, to give coloured products, the thioindogenides:



of which the most important representatives have already been considered in connection with the thioindigo dyes (pp. 574 ff).

Pyrrole group¹

PYRROLE, the nitrogen analogue of furan and thiophen, is the parent substance of a very large class of compounds, including important natural products, which has recently been developed exceedingly by synthesis. Characteristic of pyrrole compounds is the red colour which their vapour gives with a pine splint dipped in hydrochloric acid, a fact which gave rise to the name of the parent substance (pyrrole = "red oil").

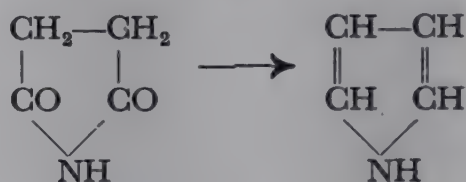
Pyrrole was detected in coal-tar early on, but particularly in so-called bone-tar, which is obtained by heating bone-meal. Anderson first prepared it in the pure state in 1858 from the latter.

Amongst the natural products which are derivatives of pyrrole may be mentioned the protein "foundation stones", proline, hydroxyproline, and tryptophan; indican, the parent substance of indigo; many alkaloids, such as nicotine, atropine, cocaine; the colouring matter of blood, and chlorophyll.

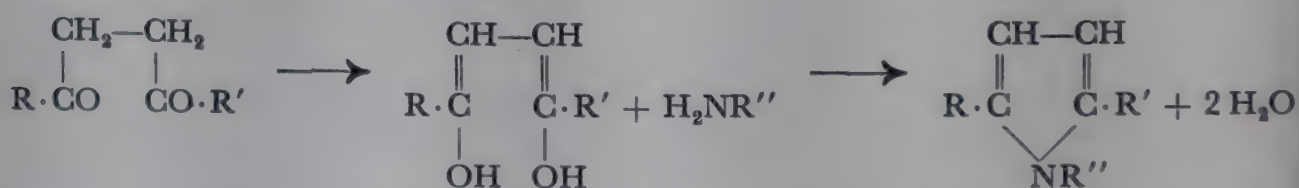
The most important discoveries in the pyrrole group are due to the work of Ciamician and Silber, A. von Baeyer, Knorr, and Hans Fischer.

A series of natural substances are available for the preparation of pyrrole compounds. Thus, for example, several homologues of pyrrole and pyrrolecarboxylic acids have been isolated by the cleavage of the colouring matters of blood and green leaves. There are, however, also various methods of preparing pyrrole derivatives synthetically:

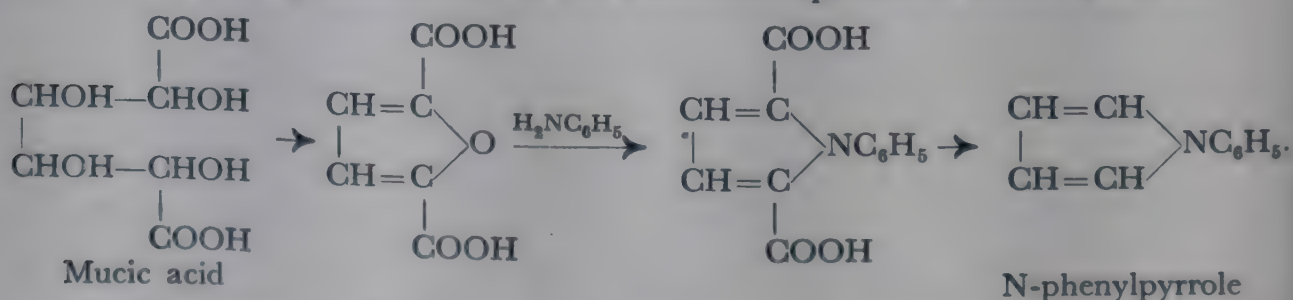
1. The distillation of succinimide with zinc dust gives pyrrole:



2. 1:4-Diketones, which have already proved to be suitable materials for the preparation of furan and thiophen compounds, give pyrrole derivatives on heating with ammonia or primary amines:



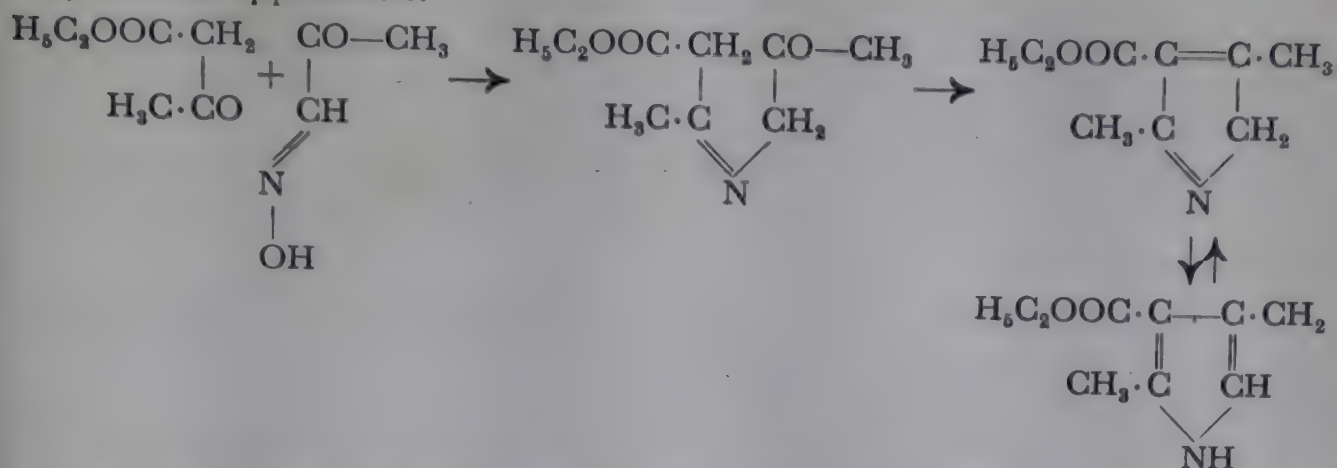
3. A similar reaction giving rise to pyrrole is the action of heat on the ammonium salts of mucic acid, or the aniline compound of mucic acid, etc.



4. The syntheses of pyrrole and its derivatives by the simultaneous reduction

¹ Review: HANS FISCHER and HANS ORTH, *Die Chemie des Pyrrols*, Bd. I, Leipzig (1934); Bd. II 1. Hälfte, Leipzig, (1937); Bd. II, 2. Hälfte, Leipzig, (1940).

of equimolecular quantities of a ketone and an isonitrosoketone are capable of very general application:

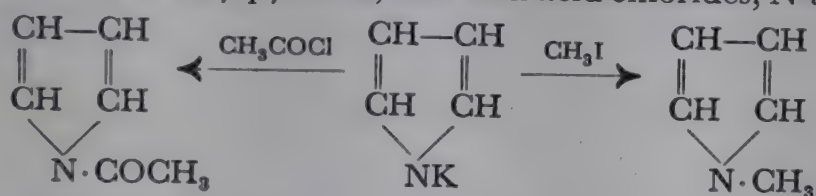


Aminoketones, produced from the isonitrosoketones, are intermediate products of the reaction.

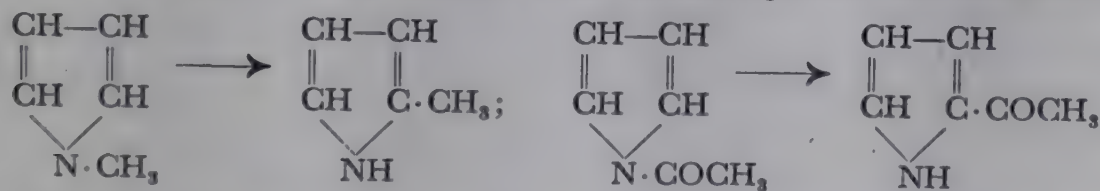
Pyrrole, when freshly distilled, is a colourless oil, with a not unpleasant smell, and which boils at 130° (corr.). In contact with air it soon becomes coloured yellow, then brown, and finally resinifies. Unattacked by alkalis, it is very readily affected by acids. First there is a red coloration, and very soon the separation of a resin ("pyrrole resin").

Pyrrole has practically no basic properties. It gives an addition product with ferrocyanic acid, and adds on hydrogen chloride in the absence of water, but it cannot be regenerated unchanged from these compounds.

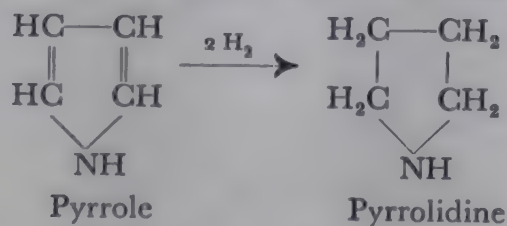
On the other hand, the imino-hydrogen of pyrrole has an acid character. It is readily substituted by potassium (but not by sodium). The solid *pyrrole-potassium* reacts with water, pyrrole being re-formed. With alkyl halides the potassium compound forms N-alkylpyrroles, and with acid chlorides, N-acyl derivatives:



In these reactions, high temperatures must be avoided, since the N-alkyl- and N-acylpyrroles possess the peculiarity of isomerizing to C-derivatives on heating. The alkyl and acyl radicals wander from the nitrogen to the α -carbon atom:



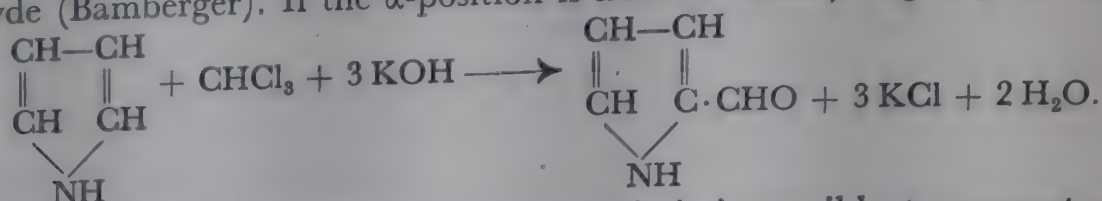
Pyrrole can be reduced to *pyrrolidine* by, for example, catalytically activated hydrogen. The reaction proceeds, however, rather sluggishly:



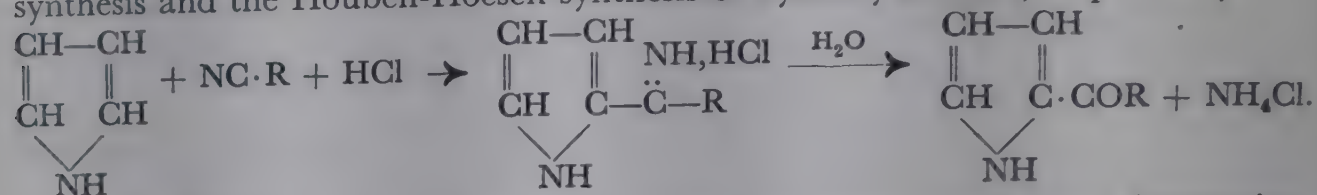
Also pyrrole and its derivatives show a marked "aromatic" character. Anal-

ogies with phenol, with which the pyrrole compounds have a whole series of chemical reactions in common, are especially noticeable.

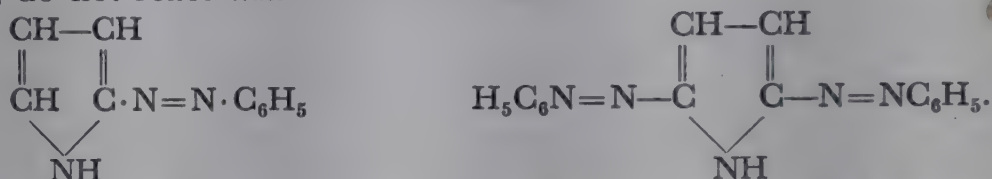
Thus, pyrrole reacts like phenol with chloroform and alkali forming an aldehyde (Bamberger). If the α -position is free the aldehyde group enters here:



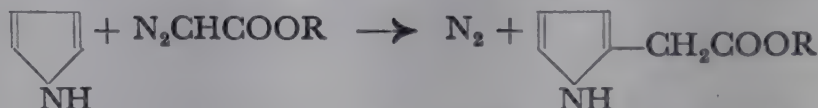
In spite of their sensitivity towards acids it is possible to convert pyrrole compounds into aldehyde and ketones (Hans Fischer) by means of hydrocyanic acid or nitriles and hydrogen chloride, similarly to the Gattermann aldehyde synthesis and the Houben-Hoesch synthesis of hydroxy-ketones, respectively:



The behaviour of pyrrole compounds towards diazonium salts is very interesting. They readily react to form azo-dyes (O. Fischer and Hepp). Pyrrole itself forms mono-azo-dyes in acid solution and bis-azo-dyes in neutral or alkaline medium, both azo-groups entering in the α -position. If the α -positions are occupied it is possible to couple pyrrole derivatives in the β -position. Tetraalkylated pyrroles, however, do not react with diazonium salts:

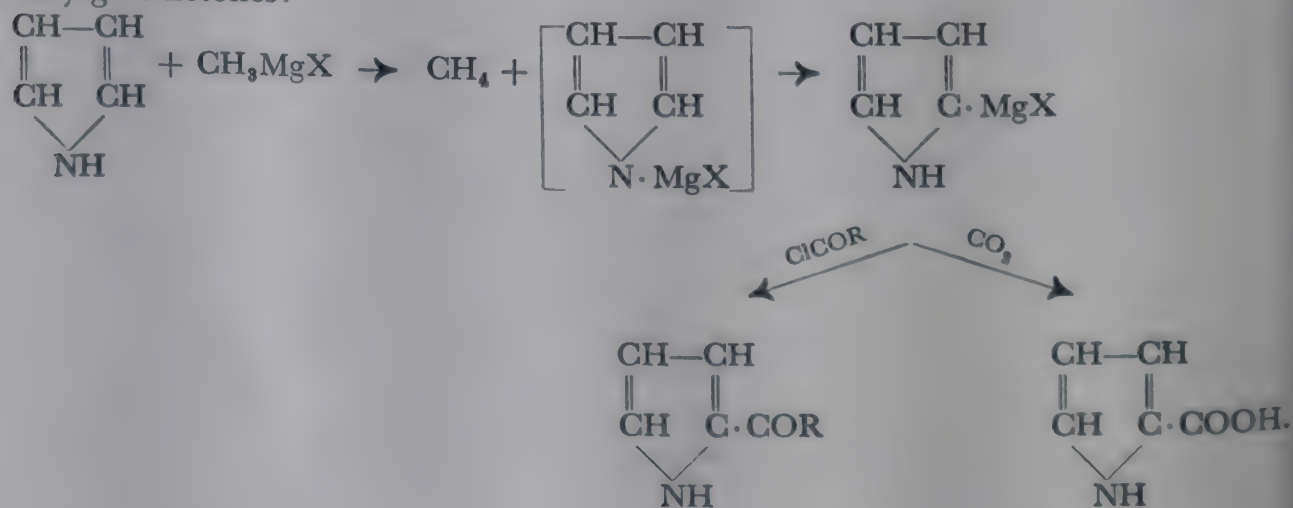


Many aliphatic diazo-compounds, such as diazoacetic ester and diazoketones, react with pyrrole and its derivatives in the presence of copper powder, forming C-substitution products:

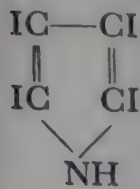


So long as an α -position in pyrrole is free, the substitution takes place there. In other cases the organic radical enters in the β -position (Nenitzescu).

As Oddo has shown, alkylmagnesium salts react with pyrroles which are not alkylated at the nitrogen atom to form *C-pyrrolylmagnesium salts*, which may be used like Grignard reagents in many kinds of syntheses. Thus, with carbon dioxide pyrrolylmagnesium salts give pyrrole- α -carboxylic acid, and with acid chlorides they give ketones:

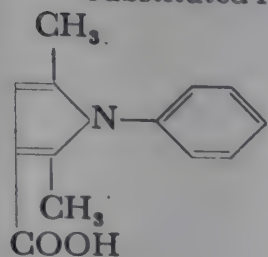


If the α, α' -positions of the pyrrole are alkylated, the substituent may also enter in the β -position by the action of the alkylmagnesium salt.



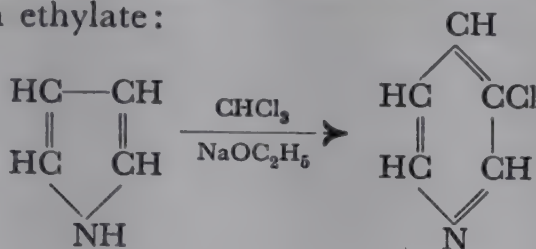
Its tendency to enter into substitution reactions is also an indication of the aromatic character of pyrrole. Halogens, e.g. iodine, substitute all pyrrole hydrogen atoms successively. Tetraiodopyrrole is used under the name *iodol* as an external disinfectant like iodoform. It has a somewhat weaker action than the latter.

Substituted N-phenylpyrroles, such as

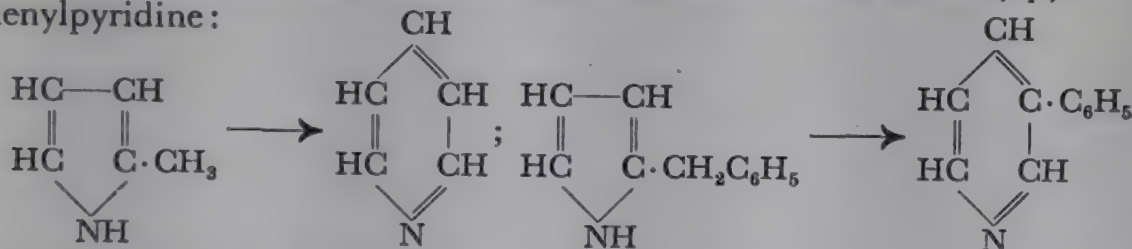


have been resolved by R. Adams into optically active compounds. In this case there is a steric isomerism analogous to that met with in the optically active biphenyl derivatives (see p. 395).

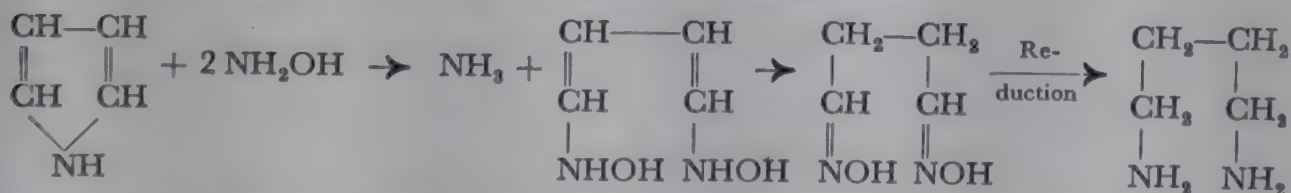
One of the most peculiar reactions of pyrroles is the *ring expansion* which these five-membered heterocyclic compounds undergo under various conditions (Ciamician). Thus, β -chloropyridine is produced when pyrrole is heated with chloroform and sodium ethylate:



If α -alkylpyrroles are passed through a red-hot tube they isomerize (with simultaneous dehydrogenation) to pyridine derivatives, the side chain entering the ring in the β -position, as shown by the conversion of α -benzylpyrrole into β -phenylpyridine:



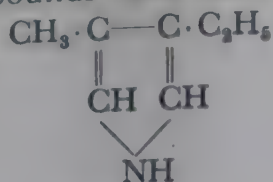
The action of hydroxylamine has been observed to give rise to a smooth *opening of the ring* of the pyrrole molecule. The dioxime of succinic dialdehyde is formed, together with ammonia (Ciamician). The former can be reduced to 1:4-diaminobutane, so that the process may be regarded, in a way, as the reverse of the formation of pyrrolidine and pyrrole from putrescine:



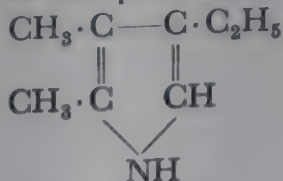
Homologues of pyrrole have been synthesized in large numbers by the above-mentioned general methods of preparation. Here, however, they are only of interest in so far as they are met with as fission products of the colouring matter of blood, chlorophyll, and bilirubin.

Hæmin from hæmoglobin, when reduced with hydrogen iodide and phos-

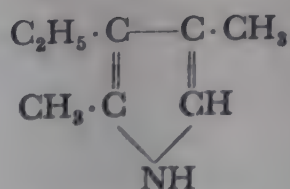
phonium iodide gives a mixture of pyrrole homologues, from which the following compounds have been isolated in the pure state:



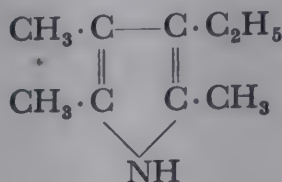
Opsopyrrole
B.p.₁₃ 74–75°
3-Methyl-4-ethyl-
pyrrole



Hæmopyrrole
2:3-Dimethyl-4-ethyl-
pyrrole;
m.p. 16–17°, b.p.₁₂ 88°



Kryptopyrrole
2:4-Dimethyl-3-ethyl-
pyrrole;
b.p.₁₃₋₁₄ 84–85°



Phyllopyrrole
2:3:5-Trimethyl-4-ethylpyrrole;
m.p. 66–67°, b.p.₁₀ 88–90°

In addition to these basic pyrroles, cleavage yields four acids of the same composition except that they have a propionic acid radical in place of the ethyl group (see p. 782). Their nomenclature is analogous to the above. All these fission products can be obtained synthetically.

Under the same conditions of fission *chlorophyll derivatives* give a mixture of pyrroles which contains similar components. Phyllopyrrole was isolated for the first time from such a mixture.

The bile pigment, *bilirubin*, also breaks down into pyrrole derivatives. From the products obtained by fusing it with caustic potash, 2:3-dimethylpyrrole, and 2:3:4-trimethylpyrrole have been isolated, and by reduction kryptopyrrole and kryptopyrrolecarboxylic acid were formed.

These results of the fission of the pigments of blood, leaves, and bile show that pyrrole compounds must play an important part in their constitution. The important work of Nencki, Piloty, Küster, Willstätter, and especially Hans Fischer, on the constitution of these pigments cannot be dealt with in detail in this book. We must confine ourselves to some references to the general structure of these complex molecules.

The colouring matter of blood. The red colouring matter of blood, or *hæmoglobin*, consists of a protein part, *globin*, and a colouring matter, *hæmochromogen*, which is a complex containing iron.

In hæmoglobin the two parts are loosely combined. In the organism it is easily converted into *oxyhæmoglobin* by absorption of oxygen, and this gives up its oxygen again and is reconverted into hæmoglobin. The transport of oxygen in the organism by the blood is carried on by this reversible process.

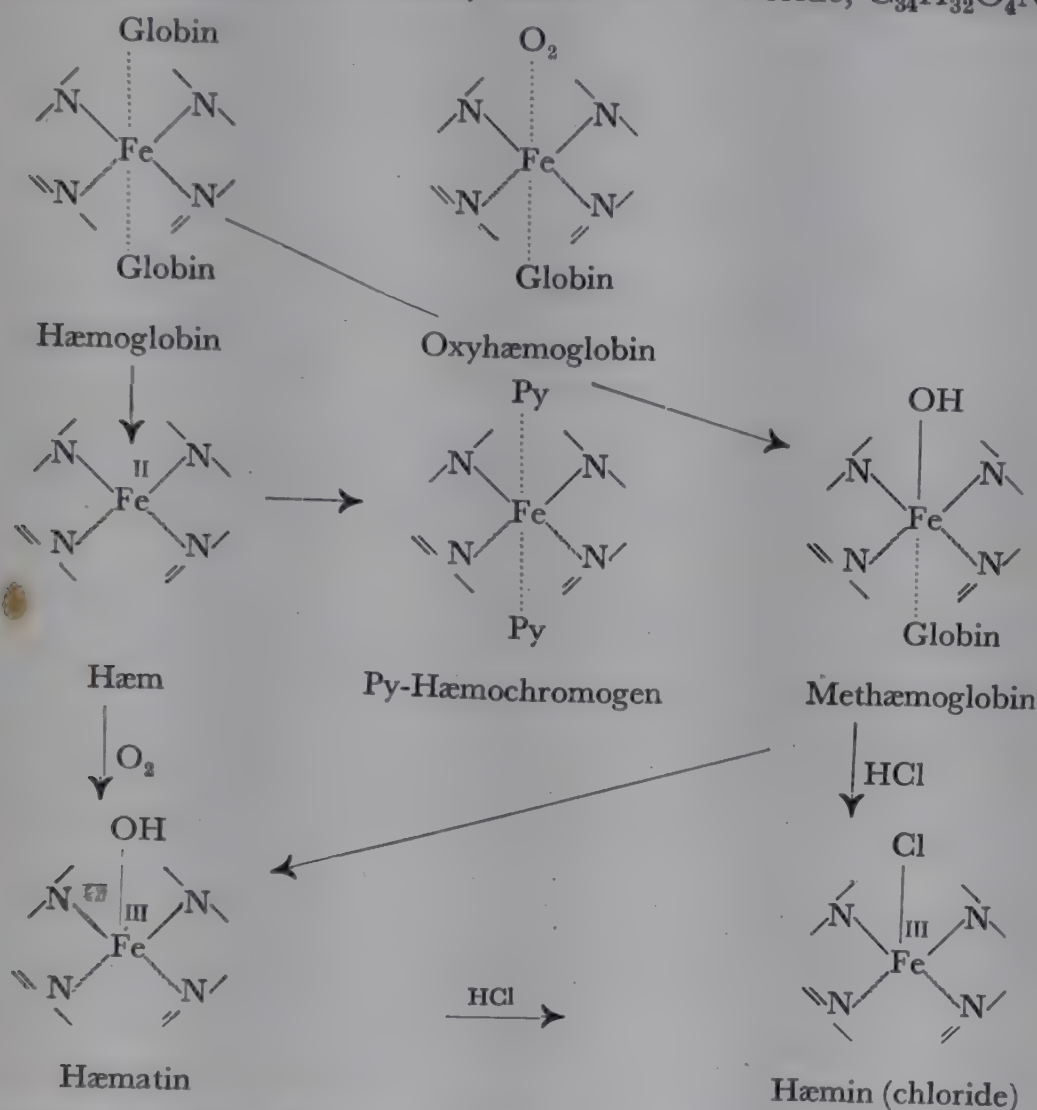
Outside the organism hæmoglobin soon changes to *methæmoglobin*, which differs from oxyhæmoglobin by having oxygen more firmly combined, and gives *hæmatin* as well as globin on fission. Hæmatin contains a hydroxyl group on the iron atom. In hæmoglobin the iron is divalent, in methæmoglobin and hæmatin it is trivalent.

The cleavage of hæmoglobin leads to globin and the easily oxidizable *hæme*,

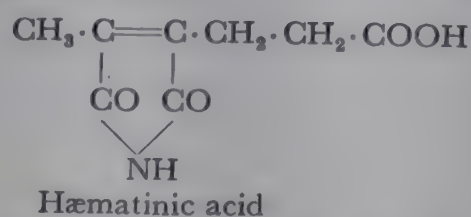
the iron of which is still divalent. Hæme is capable of combining with 2 moles of a base (e.g. pyridine), thus forming the so-called hæmochromogens. Hæmoglobin may be regarded as a hæmochromogen in which these bases are replaced by protein molecules.

On oxidation, hæme is readily converted into hæmatin (with trivalent iron); this reaction is reversible.

Hæmatin has the composition $C_{34}H_{32}O_4N_4Fe(OH)$. It forms salts with acids, which are known as *hæmins*. Ordinary hæmin is the chloride, $C_{34}H_{32}O_4N_4FeCl$.

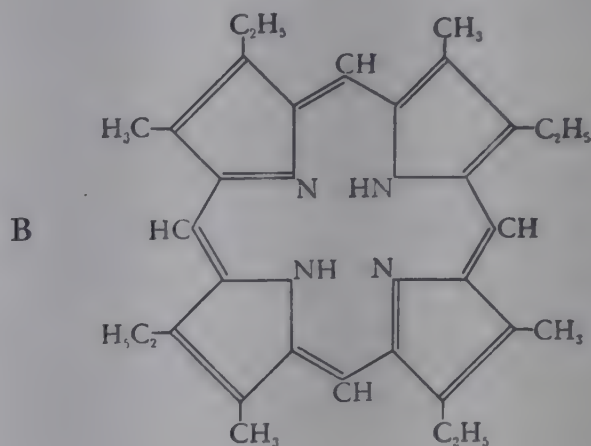
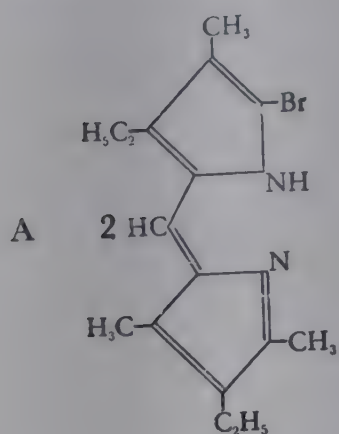


Hæmatin as well as hæmochromogen give, on removal of the iron, either protoporphyrin or the same *hæmatoporphyrin*, $C_{34}H_{36}O_6N_4$. The latter compound has acidic properties, having carboxyl groups in the molecule. On oxidative degradation it gave hæmatinic acid, which results from pyrrole nuclei. It is a very common thing to find that pyrrole derivatives, on oxidation with chromic acid, give derivatives of maleic imide:



By a series of reactions, mesoporphyrin, a reduction product of hæmatoporphyrin, and uroporphyrin (see p. 774) are degraded to ætioporphyrin, $C_{32}H_{38}N_4$. Ætioporphyrin contains four substituted pyrrole rings.

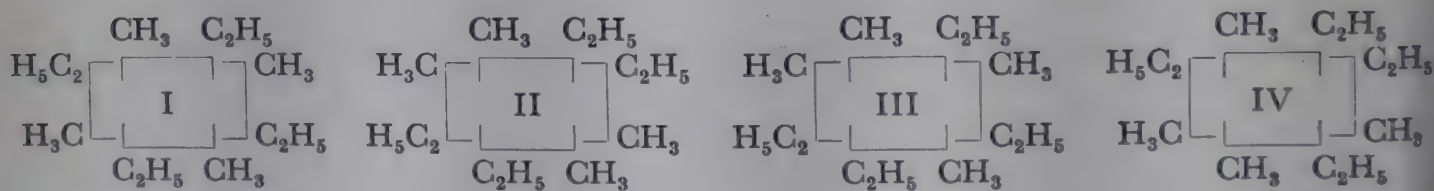
The outstanding researches of Hans Fischer, which culminated in the synthesis of this compound, have cleared up its constitution. The synthetic preparation of the ætioporphyrins has been carried out by different methods. In one of them kryptopyrrole is condensed by bromination to a methene derivative of the formula A. If this is now treated with concentrated sulphuric acid or formic acid, it is converted into ætioporphyrin I of formula B¹:



A second synthesis of ætioporphyrin depends on the reaction of β,β' -disubstituted pyrroles with glyoxal tetramethyl acetal and formic acid, and a third depends on heating α,α' -dicarboxylated dipyrromethanes in formic acid.

Further, α,α' -brominated dipyrromethenes react with α,α' -dimethylated or bromomethylated dipyrromethenes when fused together with succinic acid to give ætioporphyrins. These syntheses are very general in their application.

In this way all four possible ætioporphyrins, which differ in the positions of their methyl and ethyl side chains, have been obtained synthetically. Their formulæ may be written shortly by a "bracket system", devised by H. Fischer, as follows:



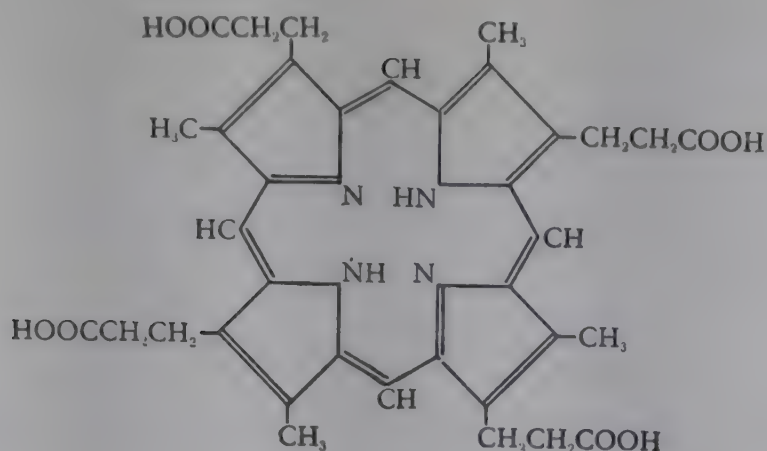
Ætioporphyrin III has proved to be identical with the compound obtained from the colouring matter of blood with regard to its absorption spectrum, its crystalline form, and all other properties.

A porphyrin, $C_{36}H_{38}N_4O_8$, occurs in the fæces and urine (*koproporphyrin*), and another has been isolated from urine (*uroporphyrin*, $C_{40}H_{38}N_4O_{16}$) (H. Fischer). All these substances have similar chemical structures, only the arrangement of side chains is different from that of hæmin; these porphyrins probably owe their origin to an independent synthesis. The isomers, kopro- and uroporphyrin III, derived from hæmin, occur in the animal organism, especially when poisoned.

Koproporphyrin has been synthesized by Hans Fischer by various methods like those mentioned above in connection with ætioporphyrin. The following

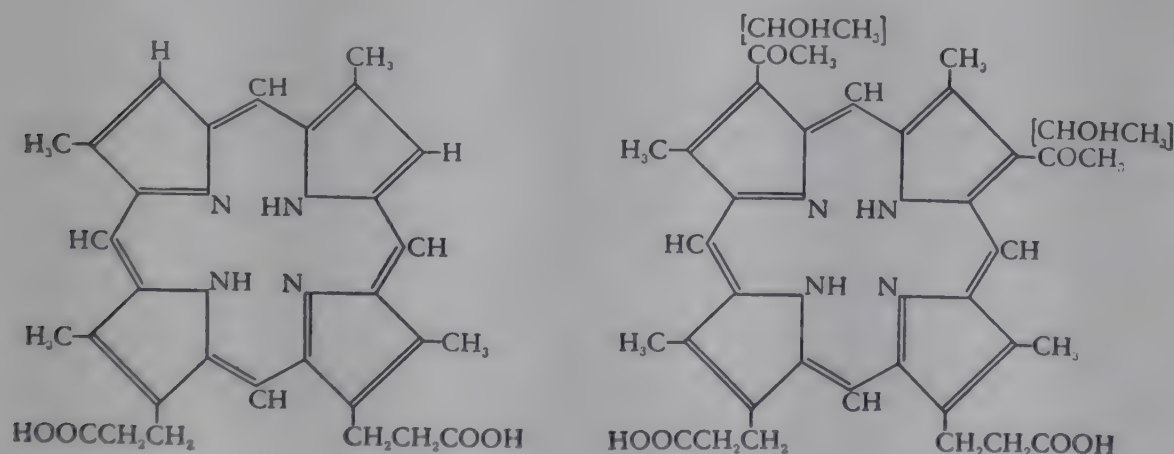
¹ Ætioporphyrin I corresponds to the formula of koproporphyrin (given below) in the arrangement of its side chains.

structure is assigned to it on the basis of these synthetic methods of preparation and its degradation products:



This shows that there is in koproporphyrin a different ætioporphyrin system from that in the colouring matter of blood. A further koproporphyrin III has been found in nature by Hijmans van den Bergh and H. Fischer, which, as is indicated by its synthesis, is derived from hæmin in the arrangement of its side chains. If each end hydrogen atom of the four ethyl radicals in the above formula of ætioporphyrin III is replaced by carboxyl, the formula of koproporphyrin III is obtained.

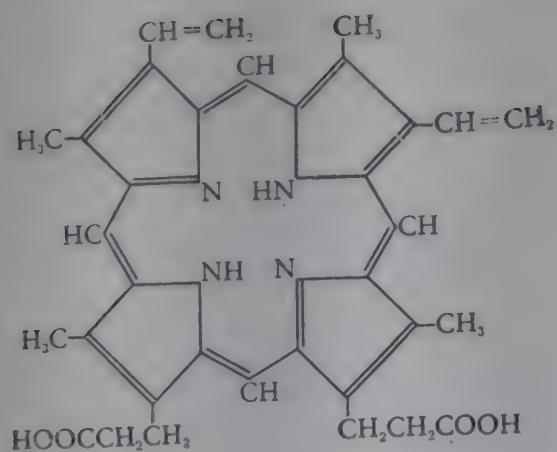
Finally, the extensive synthetic work in this group has been crowned by the synthesis of hæmato- and protoporphyrin, and hæmin. H. Fischer started with the so-called deuteroporphyrin, a porphyrin which differs from hæmin in lacking the two unsaturated side chains ($-\text{CH}:\text{CH}_2$), and which can be obtained synthetically. Two acetyl groups are introduced into deuteroporphyrin by means of acetic anhydride and stannic chloride. The diacetyl-deuteroporphyrin thus obtained is reduced by boiling with alcoholic potash, giving hæmatoporphyrin, which by the elimination of two molecules of water gives protoporphyrin. By artificially introducing iron into the synthetic protoporphyrin, hæmin is formed, which is identical with the natural product:



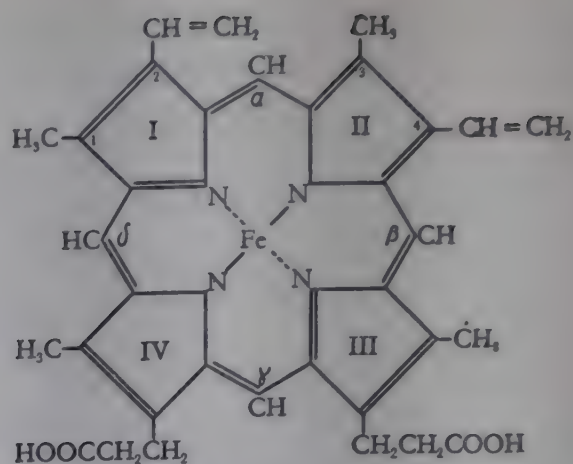
Deuteroporphyrin

Diacetyl-deuteroporphyrin

With $[\text{CHOHCH}_3] = \text{Hæmatoporphyrin}$

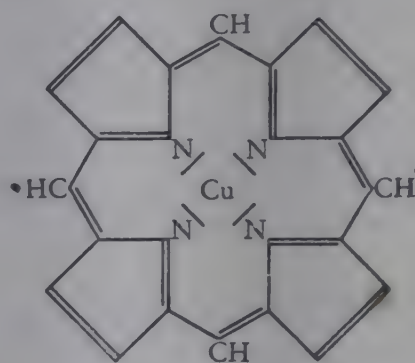
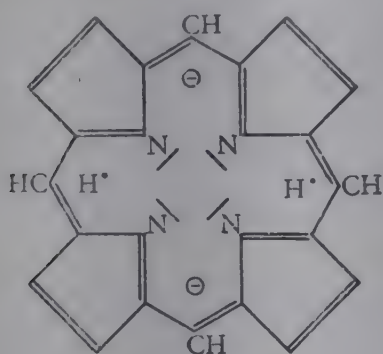


Protoporphyrin



Hæmin

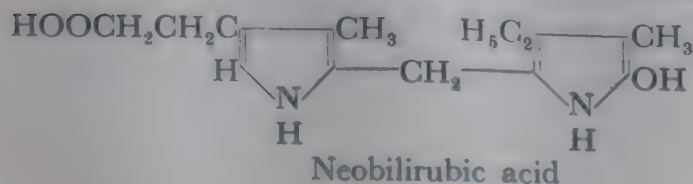
From the X-ray diffraction diagrams below it is evident that porphyrin and its complex salts possess a high degree of symmetry; they are best represented by the following electronic formulæ (F. Endermann):



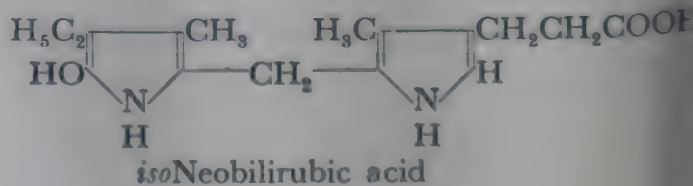
Spirographis-hæmin, which is obtained from the blood of the spirographis worm which lives in the Adriatic Sea, possesses a formula analogous to that of hæmin, but contains a formyl radical instead of a vinyl group in the 2-position. In agreement with this, it has been produced from protoporphyrin by partial oxidation with OsO_4 and H_2O_2 , the vinyl group in position 2 being oxidized to the aldehyde group.

The *cytochromes* are oxidation enzymes, related to hæmoglobin which occur, for example, in muscle, and also in yeast, etc. Cytochrome C gives hæmatoporphyrin (cf. p. 775) on cleavage with glacial acetic acid-hydrobromic acid. According to present views, cytochrome differs from hæmoglobin chiefly in that the protein component (globin fragment) is not linked alone by partial valencies to the iron. It is believed that also main valency bonds exist between side chains of the porphyrin ring and amino-acid residues of the protein. When acting as an oxidation enzyme, a reversible change of the valency of the iron in the cytochrome takes place (divalent \rightleftharpoons trivalent).

Bilirubin. The brown colouring matter of bile, *bilirubin*, $\text{C}_{33}\text{H}_{36}\text{O}_6\text{N}_4$ recalls in its composition hæmatoporphyrin. It also gives pyrrole compounds on degradation (see p. 771), some of which are identical with those isolated from hæmatoporphyrin and chlorophyll. Yet here, binuclear pyrrole derivatives, hydroxypyrromethanes, bilirubic acid, and neobilirubic acid, as well as *isobilirubic acid* and *isoneobilirubic acid* can be isolated:

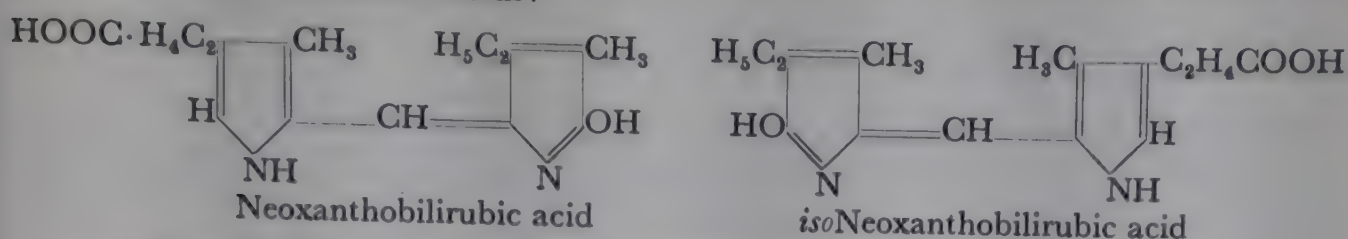


Neobilirubic acid

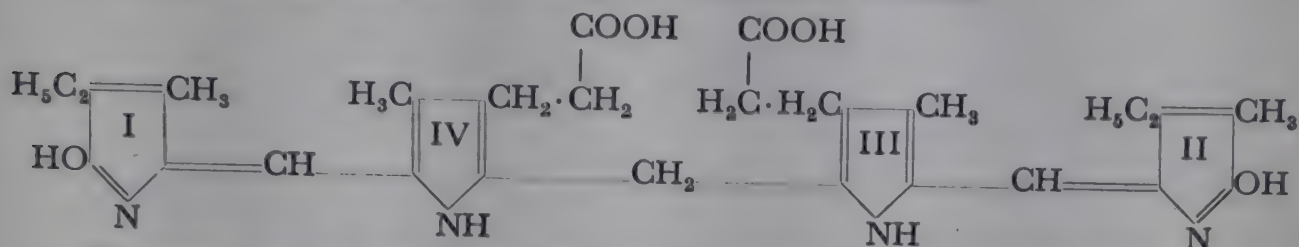


isoneobilirubic acid

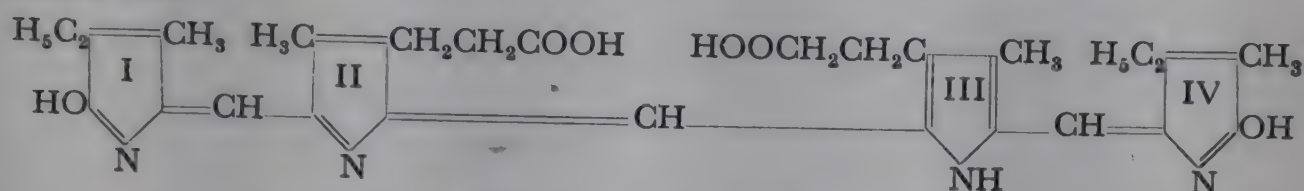
The following constitutional formulæ represent the oxidation products of neo- and isoneobilirubic acids:



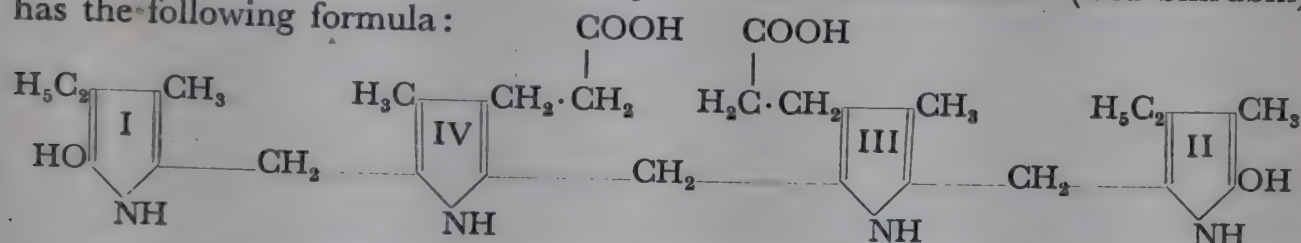
Mesobilirubin has the following constitutional formula:



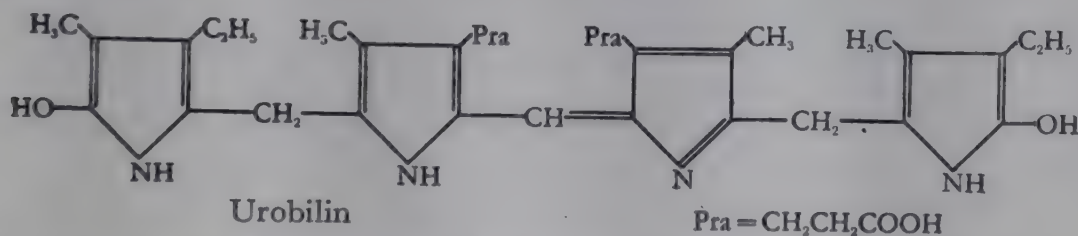
Glaucobilin, its blue dehydrogenation product, contains two hydrogen atoms less:



Mesobilirubinogen, a reduction product of mesobilirubin (and bilirubin) has the following formula:

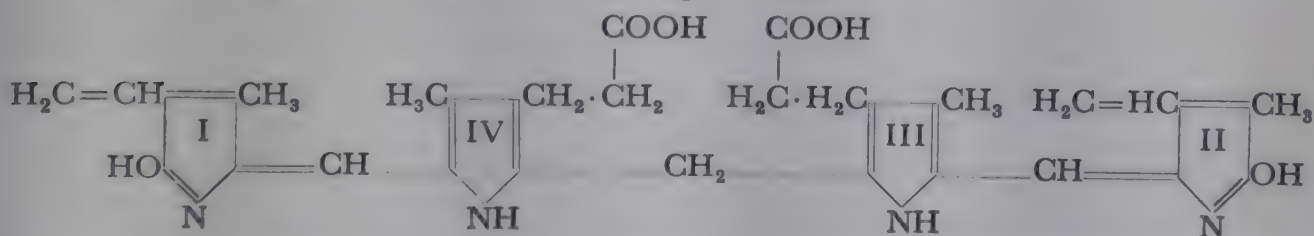


Mesobilirubinogen occurs in pathological urine in cases of liver injury, and is oxidized to urobilin:



The constitutions of mesobilirubin, glaucobilin, and mesobilirubinogen have also been proved by synthesis (W. Siedel).

Bilirubin probably has the following formula:



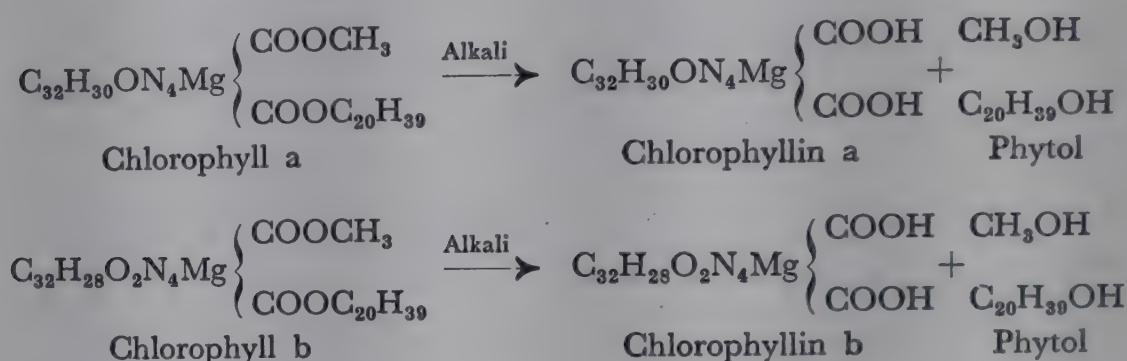
The arrangement of the side chains in bilirubin and hæmin is the same. The transition from hæmin (formula, p. 776) to bilirubin is simply explained by oxidative elimination of the α -methyne group in hæmin or protoporphyrin with the entrance of two hydroxy-groups into the pyrrole nuclei I and II, and hydrogenation of the γ -methyne group, so that the methylene group which links the two bilirubin halves is produced.

O. Warburg has accomplished this transition chemically. He obtained a green product, which R. Lemberg showed to be identical with uteroverdin ester. By carrying out Warburg's reaction with mesohæmin he obtained glaucobilin ester. In an analogous way koprohæmin is transformed into koproglaucobilin ester by fermenting yeast.

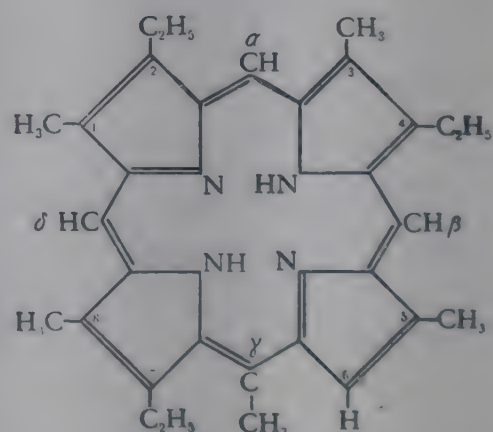
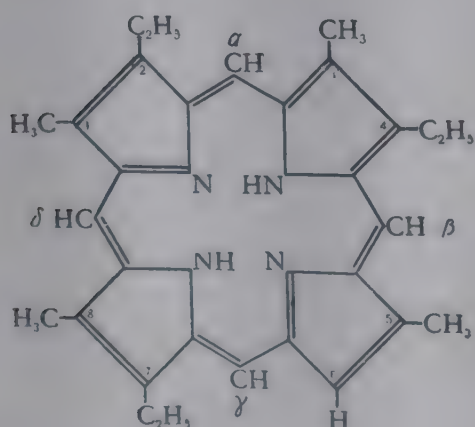
Chlorophyll¹. The green colouring matter of plants, chlorophyll, occurs in the chloroplasts. It is there accompanied by two yellow pigments, *carotene*, $C_{40}H_{56}$, and *xanthophyll*, $C_{40}H_{56}O_2$, which belong to the group of *lipochromes*² (see p. 708) which are widely distributed in plants.

The green colouring matter of leaves is not homogeneous. It consists of two components, the blue-green *chlorophyll a* and the yellow-green *chlorophyll b*, which occur in the ratio of approximately 3 to 1 (Willstätter). Both contain magnesium and have the nature of diesters.

They are hydrolysed by alkalis to the alcohols *phytol*, $C_{20}H_{39}OH$, *methyl alcohol*, and the acids *chlorophyllin a* and *b*, the magnesium being retained, according to the following scheme:



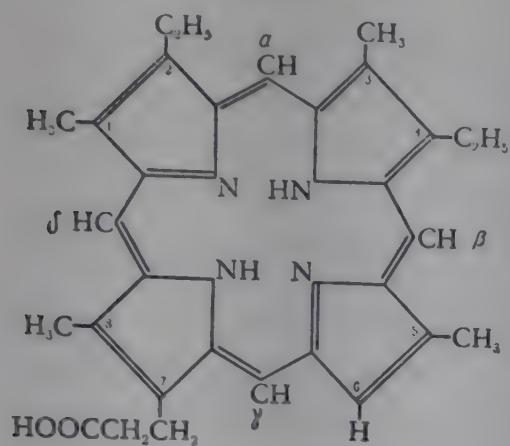
If chlorophyll or chlorophyllin is submitted to the action of alcoholates, porphyrins are produced, the compounds being two mono- and two dicarboxylic acids, phyllo- and pyrroporphyrin, and 2-vinylrhodoporphyrin and rhodoporphyrin. These porphyrins can be further decarboxylated to give ætioporphyrin (Willstätter). According to more recent investigations by H. Fischer, the chlorophyll porphyrins are derived from two ætioporphyrins which have the compositions $C_{34}H_{34}N_4$ (pyrroætioporphyrin) and $C_{31}H_{36}N_4$ (phylloætioporphyrin):



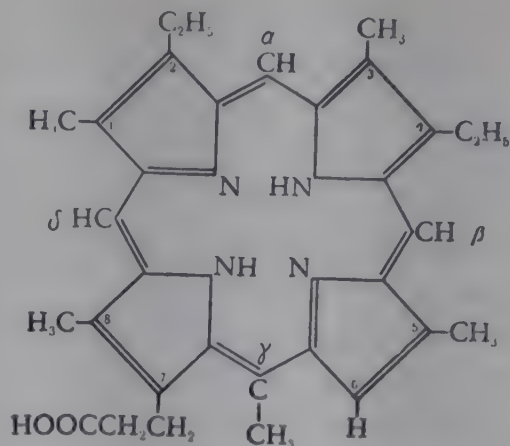
¹ See R. WILLSTÄTTER and STOLL, *Untersuchungen über Chlorophyll*, Berlin, (1913).

² LEROY S. PALMER, *Carotinoids and Related Pigments*, New York, (1922). — ZECHMEISTER, *Carotinoide*, Berlin, (1934).

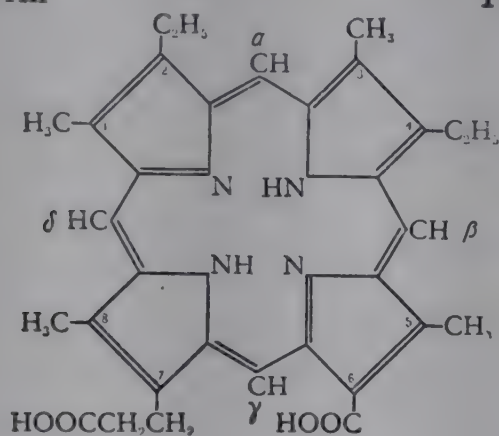
and which contain an unsubstituted methyne-group in the 6-position. Pyrro-, phyllo-, and rhodoporphyrin have been synthesized and have the following constitutional formulæ:



Pyrroporphyrin



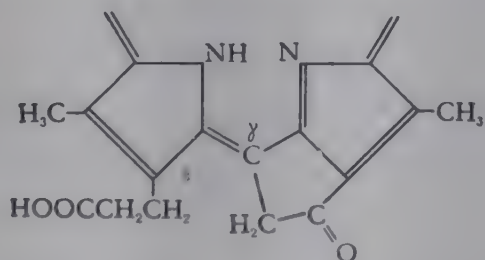
Phylloporphyrin



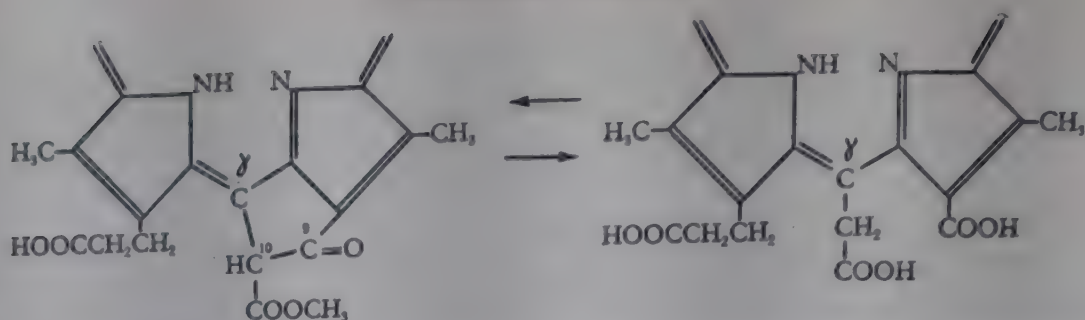
Rhodoporphyrin

Phylloporphyrin is thus a pyrroporphyrin methylated in the γ -position, and rhodoporphyrin is a pyrroporphyrin carboxylated in the 6-position.

The close relationship between these porphyrins is best shown by the conversion of pyrroporphyrin into mesoporphyrin by introducing the propionic acid radical in the 6-position. In the further investigation of chlorophyll the elucidation of the constitution and the synthesis of phylloerythrin, discovered by Löbisch and Fischler, and Marchlewsky, in bile, was of importance. On the basis of its synthesis and degradation reactions, phylloerythrin is assigned the following grouping:



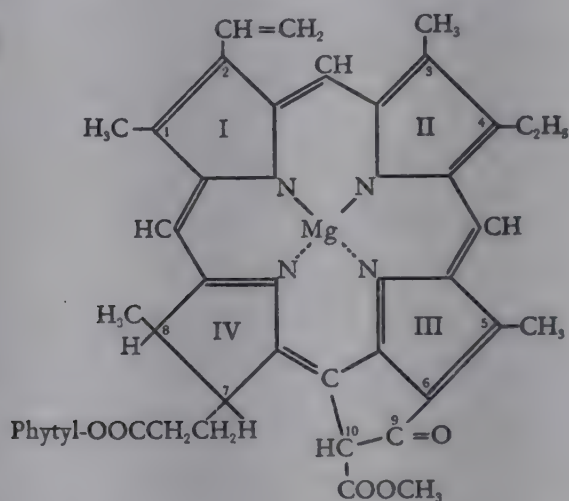
In chlorophyll a itself an esterified carboxyl group is present in the methylene group in the 10-position, which follows from the result of reducing chlorophyll and its derivatives with hydriodic acid. This produces phæoporphyrin a_5 , a phylloerythrin, which has a carbomethoxy-group in the 10-position. It has been produced synthetically. Its isocyclic ring can be very readily ruptured, chloroporphyrin e_6 being thus formed. The reaction is reversible, corresponding to the following scheme:



These reactions are also possible with chlorophyll and the phæophorbides, chlorin e being produced, which gives chlorophyllin e₆ on treatment with hydrogen iodide.

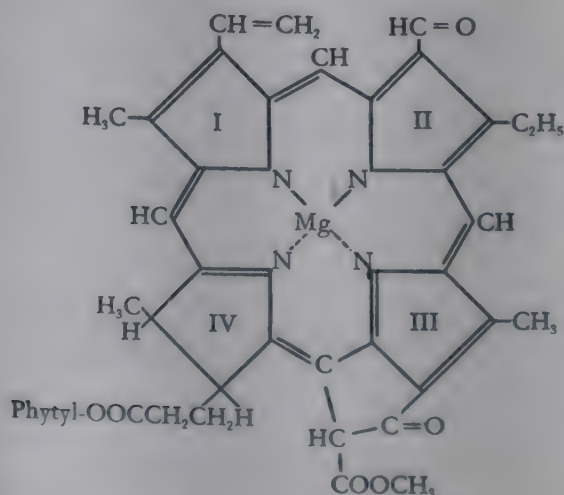
Now phæoporphyrin a₅ is isomeric with phæophorbide, as is shown by their elementary analyses and their identical energy content. The formula of phæophorbide, and thus the formula of chlorophyll, must therefore correspond with that of phæoporphyrin a₅, but the distribution of the hydrogen atoms must be different, a fact which follows from their different absorption spectra.

In chlorophyll, phæophorbide, and chlorin e, a vinyl group in the 2-position has been detected, and in addition three asymmetric carbon atoms, so that chlorophyll a has the following formula:



in which the "surplus hydrogen atoms" are in the 7-, 8-positions.

Chlorophyll b is built up in an exactly analogous way to chlorophyll a, but there is a formyl radical in place of the methyl group in position 3:

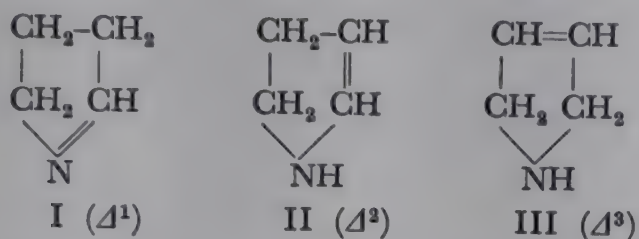


The characteristic of the two chlorophylls is thus a dihydroporphin ring with included isocyclic ring.

It is noteworthy that the purple bacteria contain a pigment which is very similar to chlorophyll, having an acetyl group in place of the vinyl group in ring I and two hydrogen atoms more in nucleus II.

Reduction products of pyrrole. Pyrrole recalls the "aromatic" compounds also in the considerable resistance it shows to hydrogenation. It is possible, however, to add on two or four hydrogen atoms, but the reactions are fairly slow.

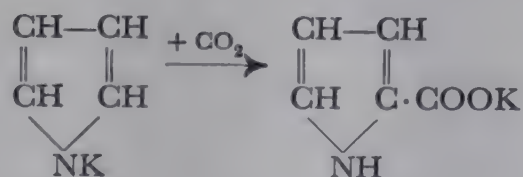
The dihydro-derivative of pyrrole, *pyrroline*, which is obtained, for example, by reducing pyrrole with zinc dust and glacial acetic acid, is a colourless liquid, boiling at 90°, which smells like an amine, and in contrast to pyrrole, has a definitely basic character. There are three formulæ to be considered for the compound:



Of these, the compound has formula III, as it is broken down to imino-diacetic acid when treated with ozone.

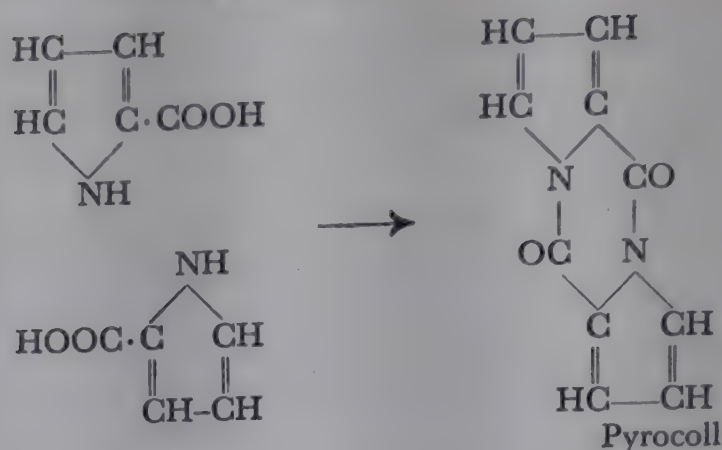
Pyrrole can be reduced to the saturated *pyrrolidine* by means of hydriodic acid and phosphorus, or of hydrogen and nickel or platinum. (Formation from putrescine, see p. 251). Pyrrolidine behaves like an aliphatic secondary base. It forms well-crystallized salts, can be alkylated to quaternary salts, reacts strongly basic, and smells like an amine (b.p. 87–88°).

Carboxylic acids of pyrrole and of its hydrogenation products. Some syntheses which lead to pyrrole- α -carboxylic acids have already been mentioned in connection with the general properties of pyrrole. (Preparation from the ammonium salts of mucic acid, and from pyrrylmagnesium salts and carbon dioxide). A further method of preparing pyrrole- α -carboxylic acid consists in heating the potassium salt of pyrrole with dry carbon dioxide, a reaction which is seen to be analogous to Kolbe's synthesis of salicylic acid. In this case, too, pyrrole behaves like a phenol:

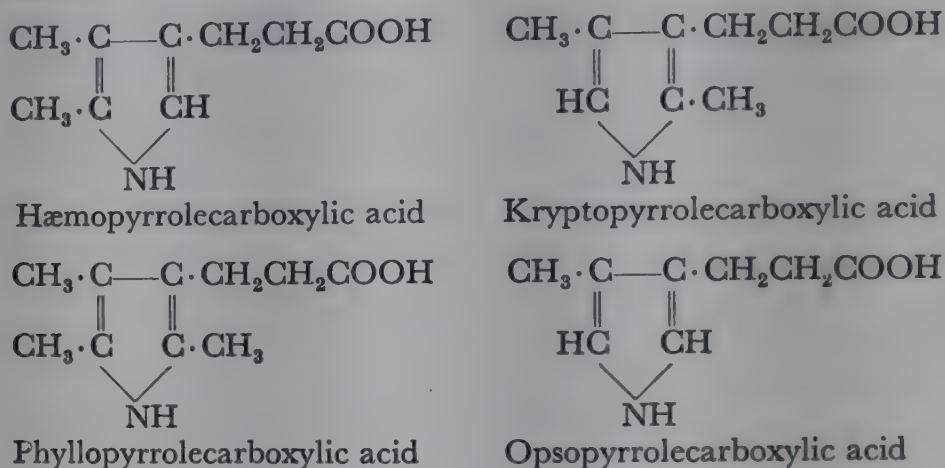


Pyrrole- α -carboxylic acid crystallizes well. On heating it breaks down into pyrrole and carbon dioxide. Its aqueous solution, which reacts acid, turns red on addition of ferric chloride.

Pyrrole- α -carboxylic acids are converted by heating with acetic anhydride into dimolecular anhydrides, the so-called *pyrocolls*. The simplest pyrocoll, which is also met with in the dry distillation of glue, where it is doubtless formed from proline by decomposition reactions, is formed as follows:



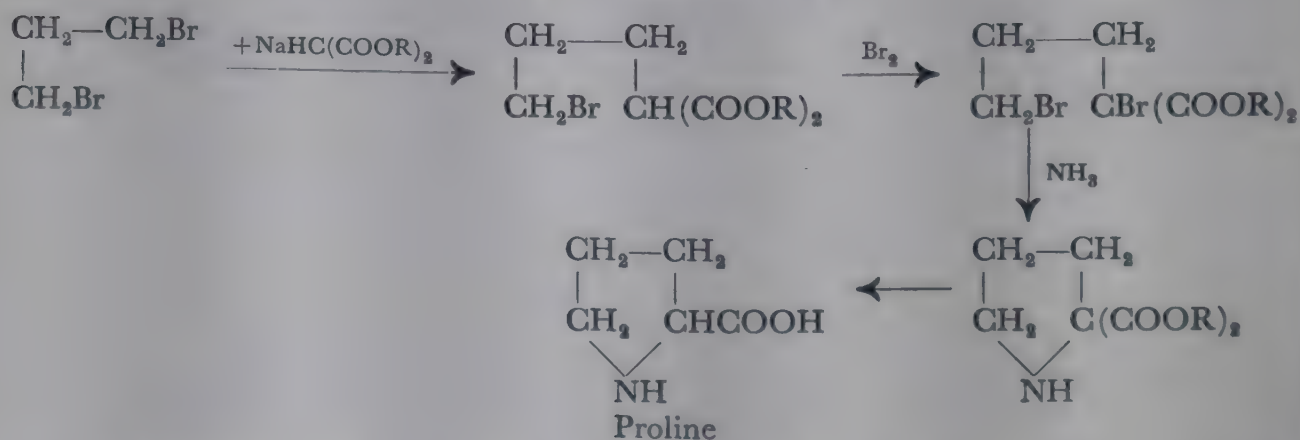
Amongst the homologous pyrrolecarboxylic acids with carboxyl in the side chain, *hæmopyrrole*-, *kryptopyrrole*-, *phyllopyrrole*-, and *opsopyrrolecarboxylic acids* are worthy of mention. They are obtained from hæmatoporphyrin and from hæmin by acid reduction:



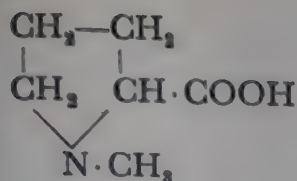
Bilirubin also gives similar compounds on fission.

Certain *carboxylic acids of pyrrolidine* are of equally great interest. Amongst them, the most important is the protein amino-acid *proline*, already known to us. In its natural form it is lævorotatory. The compound has been prepared in various ways synthetically, and the racemate has also been resolved into the optically active forms.

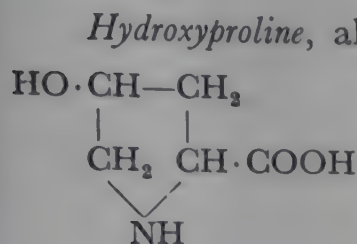
As an example the following synthesis may be given:



The active prolines melt at 220–222°, $[\alpha]_D = 81.9^\circ$. They form characteristic copper salts which are soluble in alcohol, and give a very difficultly soluble precipitate with tetrathiocyanato-dianilino-chromic acid — “rhodanilic acid”, $[\text{Cr}(\text{SCN})_4(\text{C}_6\text{H}_5\text{NH}_2)_2]\text{H}^-$ — which may be used for the detection and estimation of the prolines. The m.p. of DL-proline is about 205°; the copper salt of DL-proline does not dissolve in alcohol.



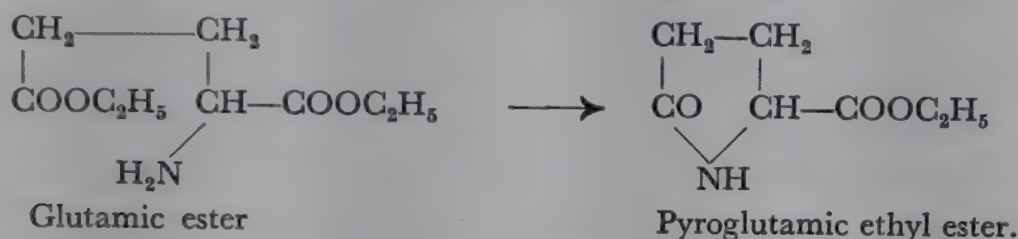
Proline methylated at the nitrogen atom is called *hygrinic acid*. It is a degradation product of the alkaloids hygrine (see p. 842), cuscohygrine (see p. 843), and nicotine (see p. 843).



Hydroxyproline, also a constituent of proteins, crystallizes particularly well, and melts at about 270° . The naturally occurring form is laevorotatory, $[\alpha]_D = -80^\circ$. In consequence of the two asymmetric carbon atoms present in the molecule there are four stereoisomerides, which have been prepared synthetically.

Tropinic acid, an oxidation product of the alkaloid tropine (see Ch. 67,1), is a dicarboxylic acid derived from pyrrolidine.

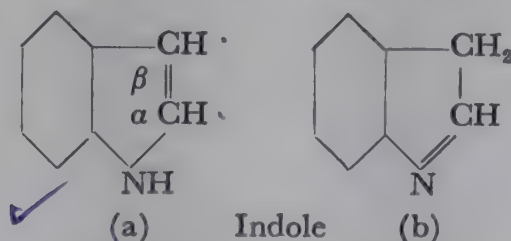
Certain pyrrolidone derivatives are very readily obtainable, particularly α' -pyrrolidone- α -carboxylic acid (pyroglutamic acid) of which the ester is formed even by warming the ester of glutamic acid:



The compound is a solid and crystallizes well (m.p. of the active acid, $158-160^\circ$; $[\alpha]_D = -11.5^\circ$). One of the higher homologues, *ecgoninic acid*, which is produced by the oxidation of ecgonine (see Ch. 67,2), will be met with later.

Indole group¹

The indole molecule consists of a benzene nucleus condensed in the *ortho*-position with a pyrrole ring. Its structure is analogous to that of coumarone. In addition to the formula (a), however, the tautomeric structure (b), in which there is a reactive methylene group, must also be considered. In many reactions the compound reacts according to this "indolenine formula" (b):

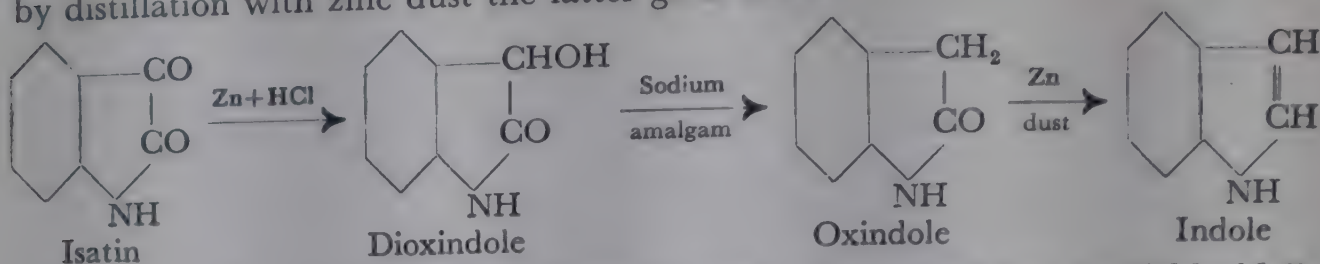


Indole compounds occur in nature fairly frequently. Thus, *indole* itself is a constituent of jasmine- and orange-blossom oils. β -*Methylindole* (*skatole*) is the compound giving the smell to faeces, occurring also in the intestines, in civet, and in various plants. In proteins, the indole complex occurs in tryptophan (see p. 786), and the glycoside, indican, the parent substance of the indigo dye, is widely spread in plants furnishing indigo.

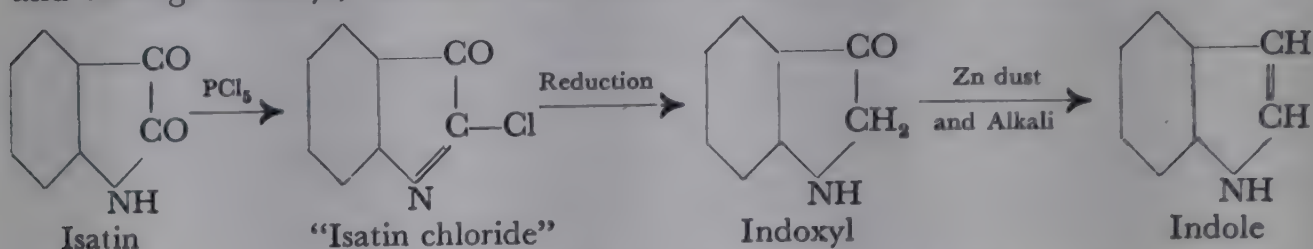
Many methods are known for the artificial preparation of indole and its derivatives, but none of these syntheses make the compounds very easily obtainable.

¹ GUSTAV HELLER, *Über Isatin, Isatyl, Dioxindol und Indophenin*, Stuttgart, (1931).

A. von Baeyer first obtained indole from indigo (q.v.). Isatin (see p. 568), the oxidation product of indigo, can be reduced to dioxindole and oxindole, and by distillation with zinc dust the latter gives indole:

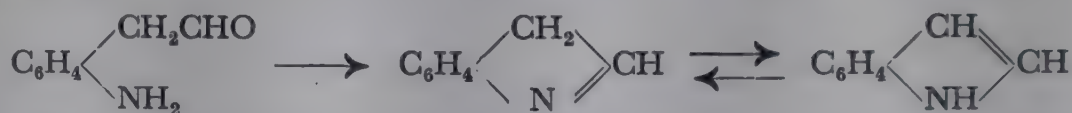


A second method starts with isatin, which is converted into its "chloride", and through indoxyl, to indole the parent compound of the series:



Since indoxyl (see p. 571) is produced technically by fusing phenylglycine-*o*-carboxylic acid with alkali, and its reduction to indole presents no difficulty, this method for making indole is probably the one most commonly used at present.

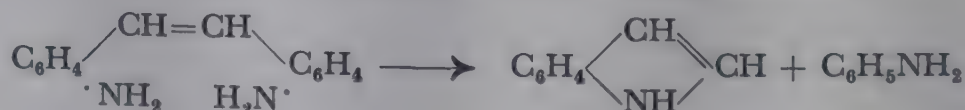
All syntheses of indole start with aromatic compounds, and the five-membered, nitrogen-containing nucleus is attached by ring-closure. In this way indole may also be made by the intramolecular elimination of water from *o*-aminophenyl-acetaldehyde:



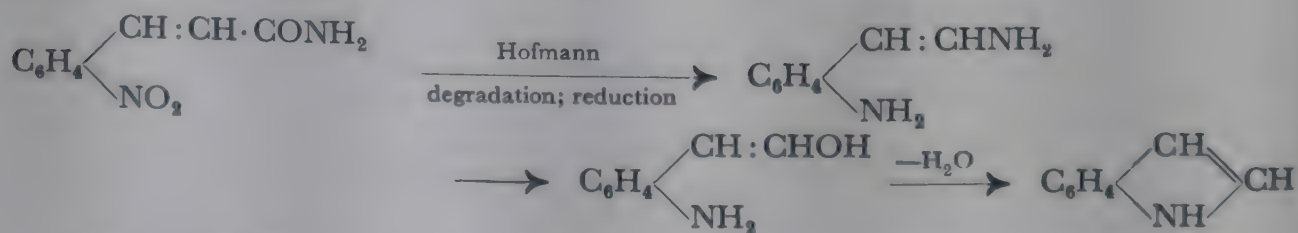
or from *N*-formyl-*o*-toluidine by heating with potassamide or potassium methylate:



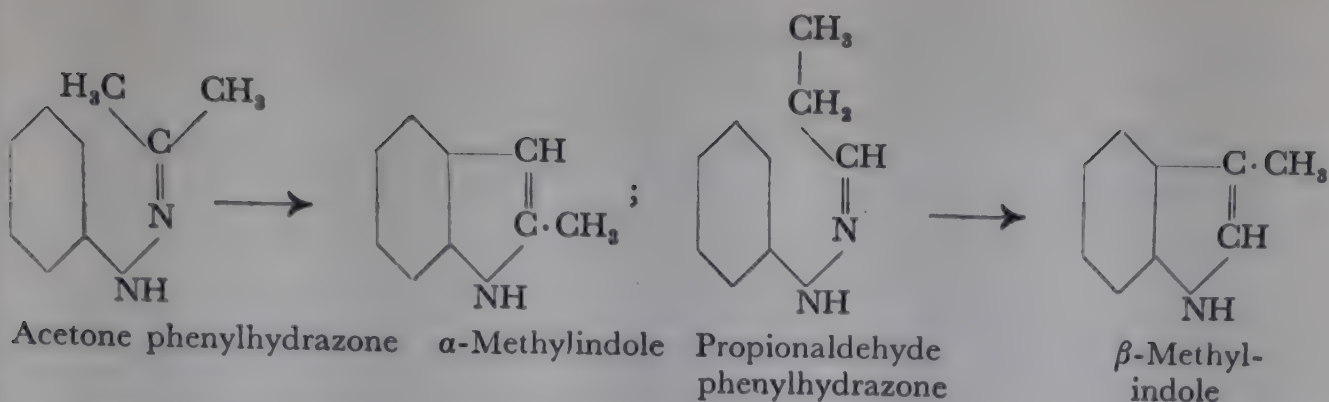
or from *o,o'*-diaminostilbene by heating with its hydrochloride:



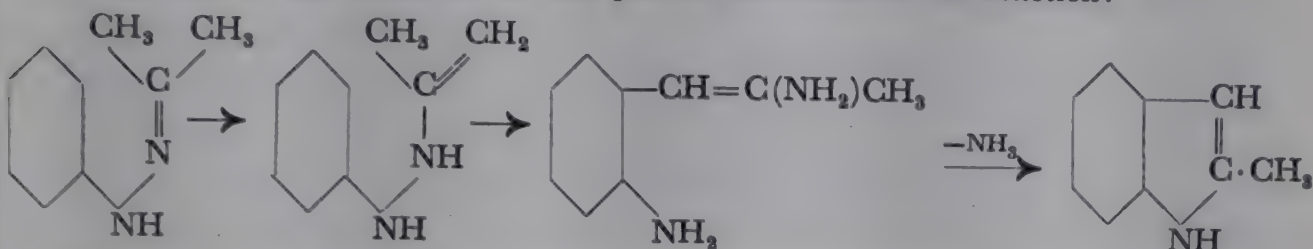
or from *o*-nitrocinnamic acid amide:



A method devised by E. Fischer is suitable particularly for the preparation of homologues of indole. It consists in heating the phenylhydrazones of aldehydes or ketones with zinc chloride (or cuprous chloride or bromide) to high temperatures. The nitrogen atom farther from the benzene nucleus is eliminated as ammonia:

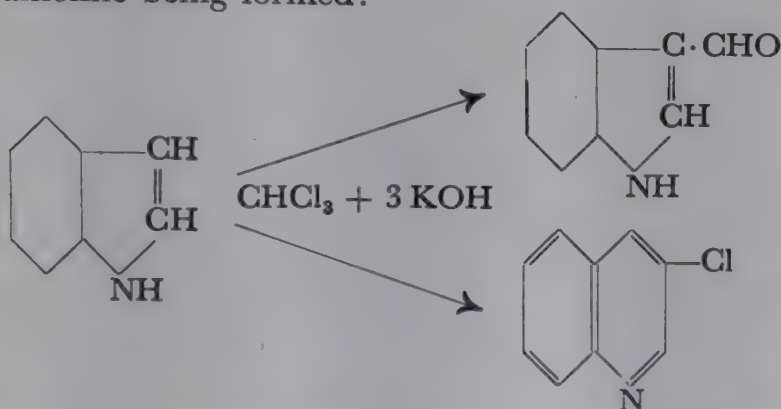


This peculiar reaction may perhaps be explained by assuming a kind of *o*-benzidine rearrangement to take place in the first part of the course of the reaction:



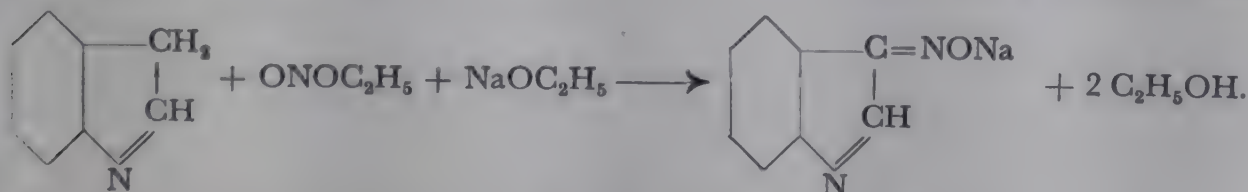
In chemical properties indole shows several similarities with pyrrole. Like the latter it possesses scarcely any basic properties. However, a picrate exists. On the other hand, it forms a sodium and a potassium salt (sodium- and potassium-indole). It is less sensitive to acids than pyrrole, being resinified by them only on heating.

By the action of chloroform and alkali on indole, β -indolealdehyde is formed. Simultaneously another portion reacts, as in the pyrrole series, with ring expansion, β -chloroquinoline being formed:



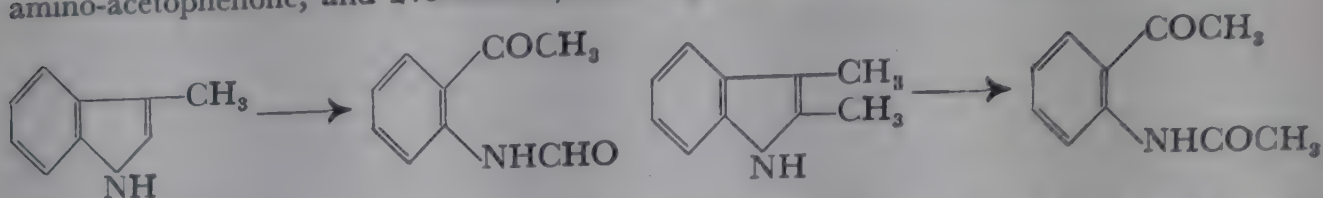
It is also possible to pass to the quinoline series from the α -alkylindoles, which undergo ring expansion on passing through a red-hot tube.

With Grignard reagents indole reacts to form indylmagnesium salts. Their further reactions give chiefly β -indole derivatives. Various reactions of indole support the "indolenine formula" (i.e. the presence of a reactive methylene group in the molecule). The formation of β -isonitroso-derivatives on treatment with alkyl nitrite and sodium ethylate in alkaline medium (nitrosation) may be mentioned:



Indole and its derivatives are readily degraded by ozone giving characteristic products,

which are formed by splitting of the pyrrole ring. Thus, 3-methylindole produces *o*-form-amino-acetophenone, and 2:3-dimethylindole gives *o*-acetamino-acetophenone:



Indole crystallizes in shining leaflets, melting at 52°; it boils at 253° (762 mm) (corr.). The red, well crystallized picrate is characteristic. When impure, indole possesses an unpleasant smell, but in the purest preparations it has a flower-like odour. It finds extensive use in perfumery.

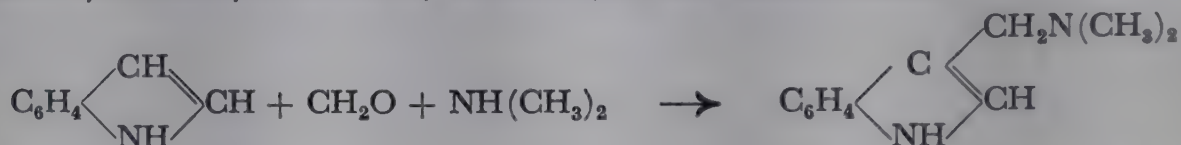
The considerable amount of indole contained in the higher boiling fractions of coal-tar is worthy of mention.

β -Methylindole, or *skatole*, of which the occurrence in the intestines and in faeces has already been mentioned, appears there as a degradation product of tryptophan, a constituent of proteins. Intermediate products in this decomposition of tryptophan, which is brought about by bacteria causing decay, are *skatole-acetic acid* (β -indolylpropionic acid), and *skatolecarboxylic acid* (β -indolylacetic acid).

Skatole has a repulsive smell, especially when impure. It melts at 95°, and boils at 265° (755 mm).

Indole-3-acetic acid (β -indolylacetic acid) has been recognized as a growth-factor for plants, and as such is called *heteroauxin* (Kögl).

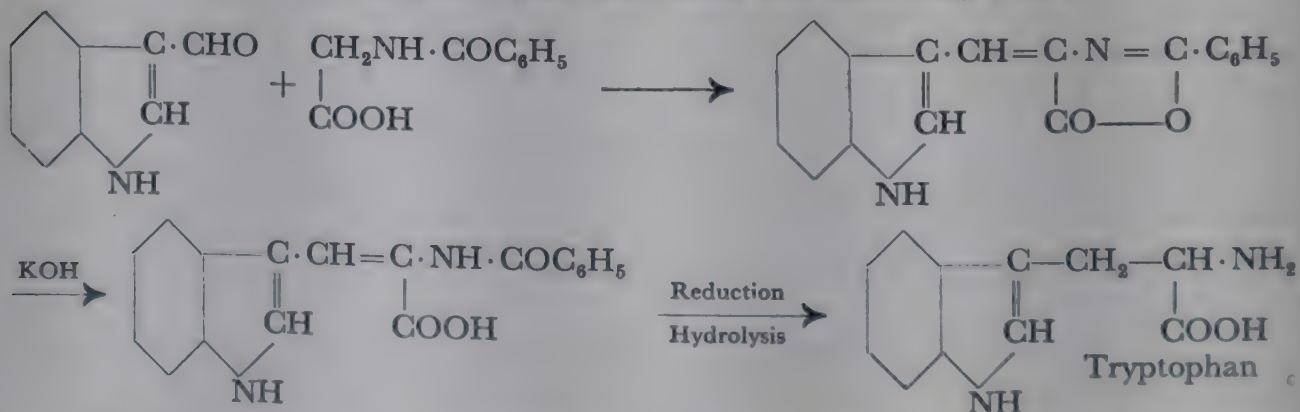
Gramine, occurring in *gramineæ*, is β -(dimethylaminomethyl)-indole, and may be prepared synthetically from indole, formaldehyde, and dimethylamine:



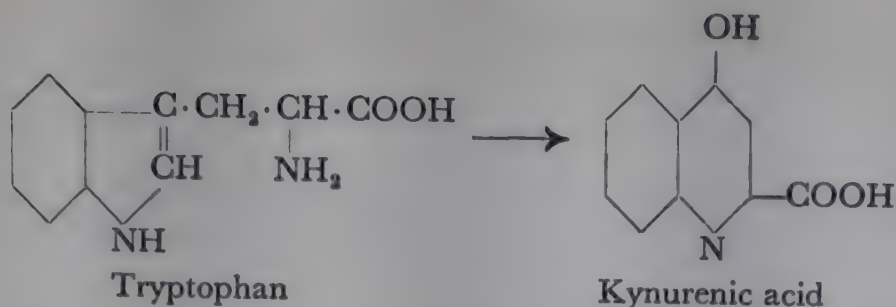
Tryptophan is an integral constituent of many kinds of protein, in which, however, it usually only occurs in small quantities. Its presence can be detected by various colour reactions which are characteristic for this amino-acid.

It is destroyed by the acid hydrolysis of the proteins, but by the enzymic fission of the protein it can be isolated in the *lævorotatory* form.

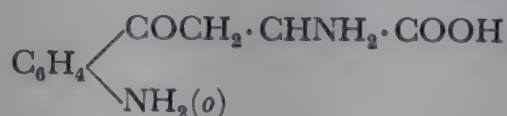
The constitution of tryptophan is proved by its synthesis, which starts with β -indolealdehyde and hippuric acid and takes the following course:



The conversion of tryptophan into γ -hydroxyquinoline- α -carboxylic acid, or *kynurenic acid*, in the organism of the dog, is of physiological interest. Kynurenic acid is thus found as a normal excretion product in the urine of dogs. Its production from tryptophan means that a ring-expansion of the five-membered indole nucleus has taken place:

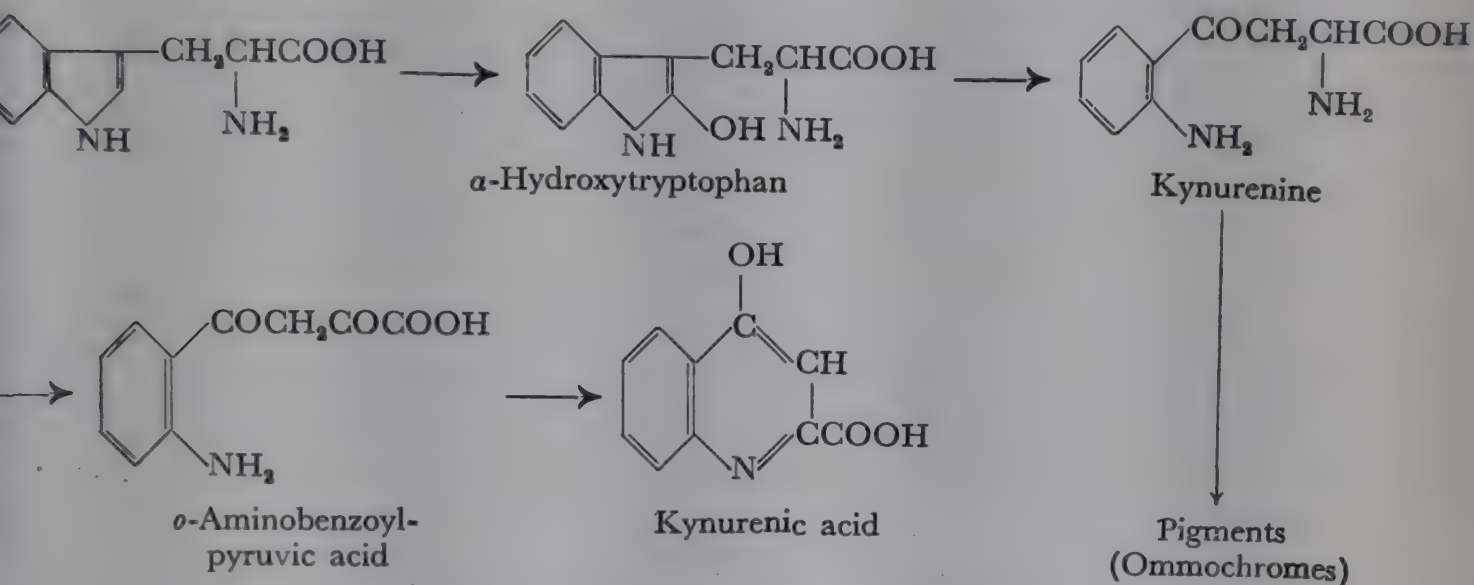


Another metabolic product, kynurenine, has been observed in the urine of rabbits fed on L-tryptophan.



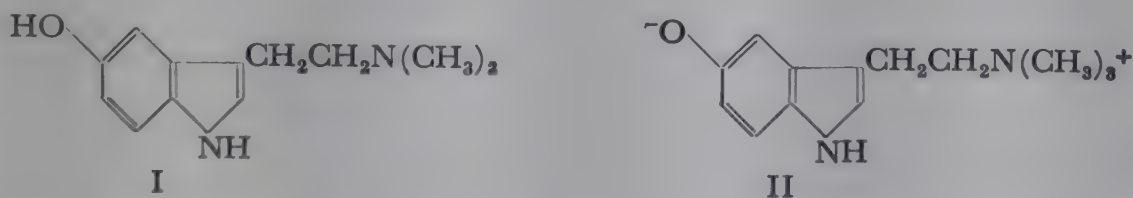
It has the interesting property of promoting the formation of eye-pigment in insects (Butenandt).

The formation of kynurenine from tryptophan and the latter's further degradation to kynurenic acid probably take place through the following stages:

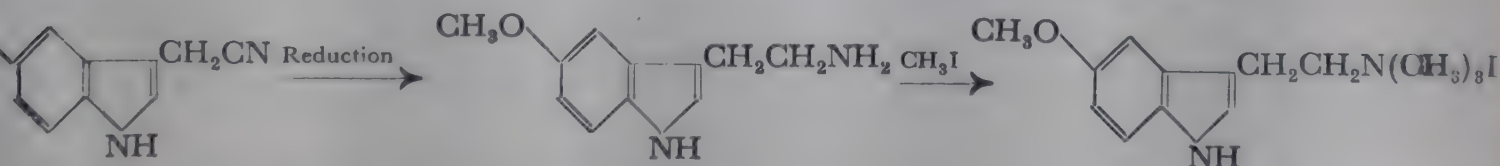


The betaine of tryptophan is identical with *hypaphorine* from the Javanese tree *Erythrina hypaphorus*. N-Methyltryptophan ("abrine") occurs in *Abrus praeatorius*. α -Hydroxytryptophan as well as cystine, hydroxyproline, and alanine occur in the poison phalloidine, which is obtained from the Death Cap (*Amanita phalloides*).

Both Wieland, and Jensen and Chen have isolated indole derivatives from the skin secretions of toads. *Bufotenine* is 5-hydroxy-3-(dimethylaminoethyl)-indole (I). *Bufotenidine* is the corresponding betaine (II):



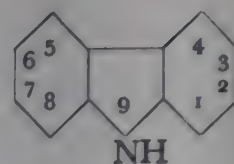
O-Methylbufotenine methiodide has been obtained synthetically in the following way:



Its hydrolysis with aluminium chloride leads to bufotenine.

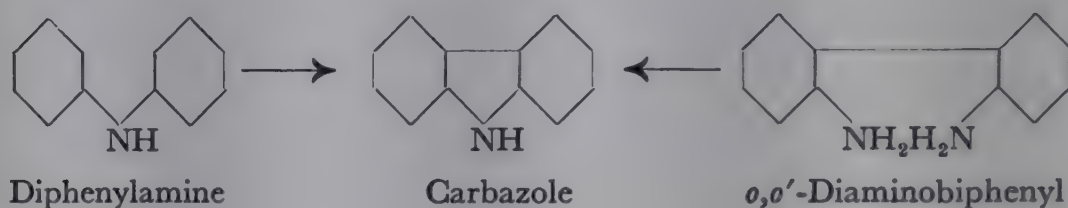
About the interesting and technically important *keto-derivatives* of indole, *isatin*, *dioxindole*, *oxindole*, and *indoxyl*, see p. 784.

Carbazole. In *carbazole* there is a tricyclic system consisting of a pyrrole ring with two benzene nuclei condensed in the *ortho*-positions.



It is found in considerable quantities in coal-tar, especially in the "anthracene oil" fraction. If this is distilled with the addition of caustic potash, the potassium salt of carbazole remains behind.

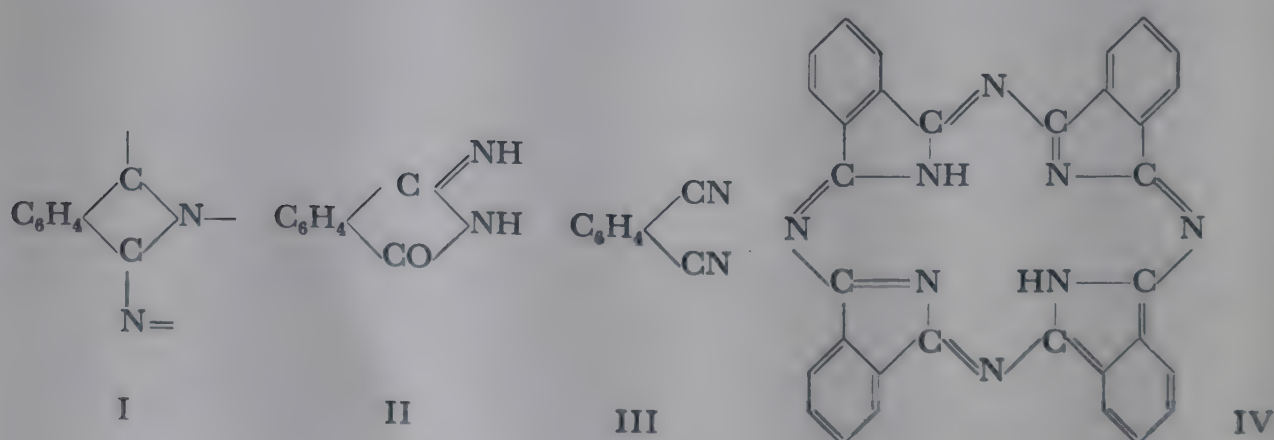
Various straightforward syntheses are known which leave no doubt as to the constitution of the compound. Thus, carbazole is formed if diphenylamine vapour is passed through a red-hot tube, or if *o,o'*-diaminobiphenyl is heated with hydrochloric or sulphuric acid.



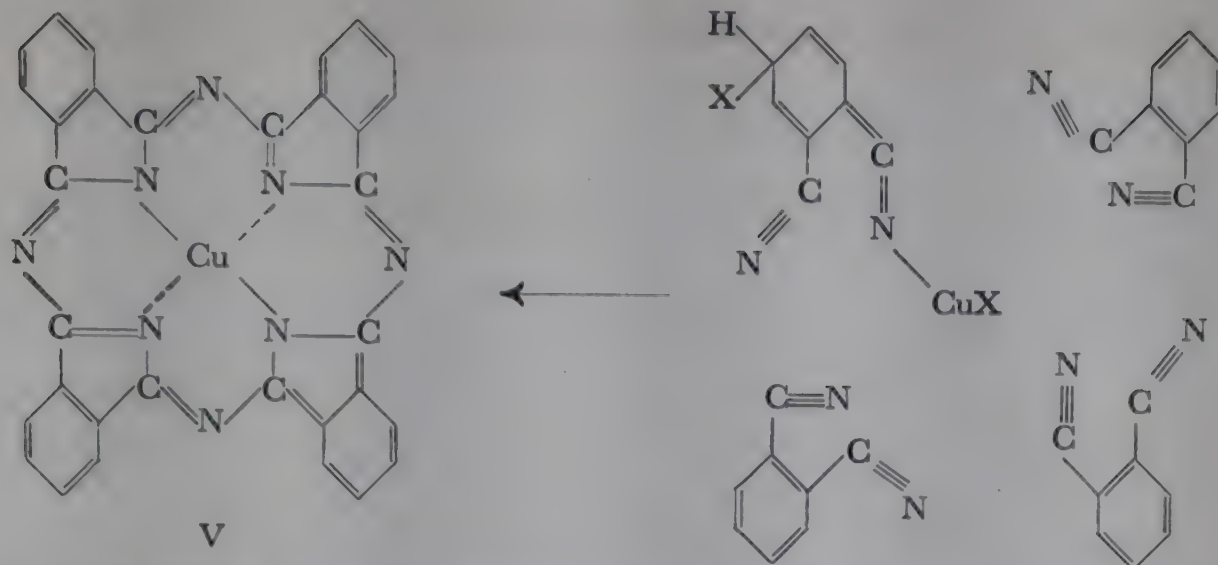
Carbazole melts at 238°, and boils at 354–355° (corr.). It forms a difficultly-soluble, characteristic picrate and perchlorate. As a secondary amine it gives a N-nitroso-compound.

Carbazole is an important substance from the technical point of view. It is used as a starting material for the manufacture of dyes, e.g. for the synthesis of Hydron blue (see p. 629).

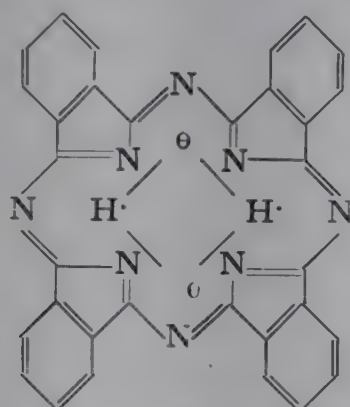
Phthalocyanines. Interesting blue to green, very fast dyes, which may be regarded as derivatives of an *isoindole*-compound I. have been discovered by I. instead and Lowe, and called the "phthalocyanines". De Diesbach had already obtained them earlier on. They are formed by the action of metals or metal salts (Mg, MgO, Cu, Cu₂Cl₂, etc.) on *o*-cyanobenzamide, iminophthalimide (II), or phthalonitrile (III), and contain metal atoms combined in a complex. Formula IV has been proposed for the metal-free parent substance:



The structural formula of the copper salt is shown below (V). The polymerization process of phthalonitrile may be represented roughly as follows:



On the basis of the X-ray diffraction pattern the following electronic formula⁻ has been proposed for phthalocyanine:



Since the phthalocyanines have a skeleton ring system which recalls that of the porphins they are sometimes called *porphyrazines*. Compound IV would be called tetrabenzoporphyrazine. The porphyrazines correspond with the iminoporphyrins in the porphyrin series. The latter are porphyrins in which the methine groups have been replaced by nitrogen.

There are a number of different phthalocyanines on the market including dyestuffs chlorinated in the benzene nuclei. The phthalocyanines have acquired great technical importance owing to their fastness, beauty, and intensity of colour. They rival the best mineral pigments, and are employed, e.g. instead of ultramarine, and in place of inorganic colours, for painting the walls and fronts of houses, in printing, and for the colouring of paper, plastics, lacquers, and soap.

CHAPTER 60

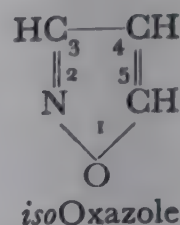
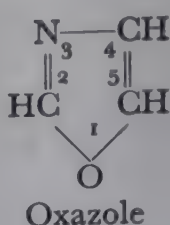
FIVE-MEMBERED HETEROCYCLIC RINGS WITH TWO OR MORE HETERO-ATOMS

The compounds of this class, which have an *aromatic* character, contain always one or more nitrogen atoms in the heterocyclic nucleus. They are known as "azoles", and differ in the nature of their other hetero-atoms: *oxazoles*, *thiazoles*, *imidazoles*, *pyrazoles*, *triazoles* (with three N atoms), *tetrazoles* (with four N atoms), etc.

A very large number of compounds is known which fall into this class. Most of them are obtained synthetically. There are, however, some naturally occurring products among them, particularly those of the imidazole type. In this book we must limit ourselves to the consideration of the most important parent substances of this class of compound.

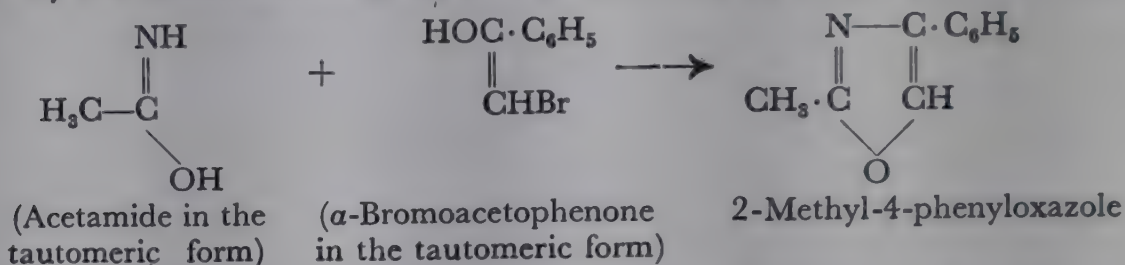
A. Five-membered heterocyclic rings with two hetero-atoms

Oxazole derivatives. If a —CH group of furan is imagined to be replaced by a nitrogen atom, the heterocyclic rings known as oxazole and isoxazole are obtained:

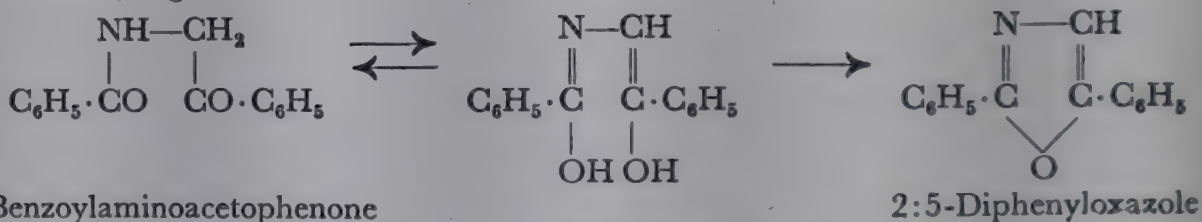


Oxazole itself has only recently been prepared (b.p. 69–70°). Its derivatives can be synthesized in various ways. Thus, oxazole derivatives are obtained:

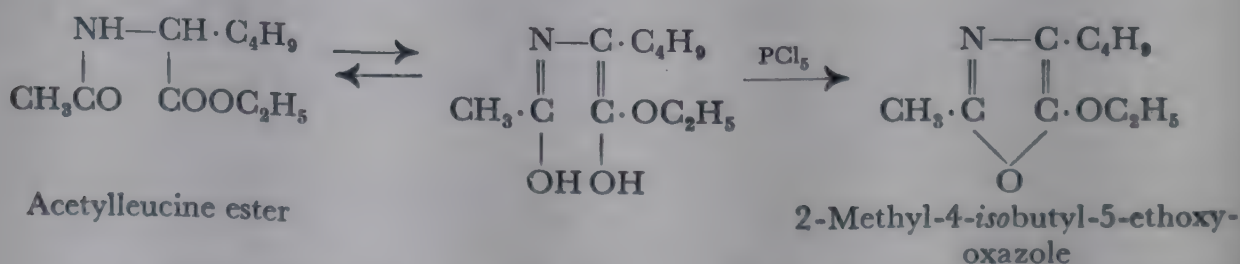
1. By the condensation of an acid amide with an α -halogenated ketone:



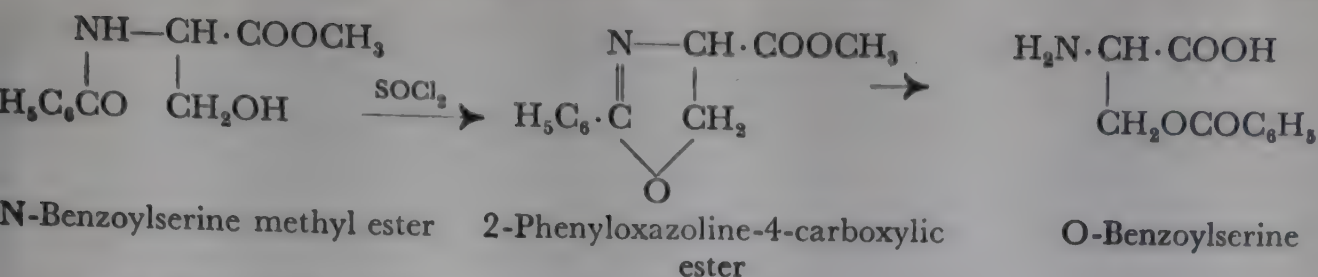
2. By the action of phosphorus pentachloride or thionyl chloride on acylaminoketones, e.g.:



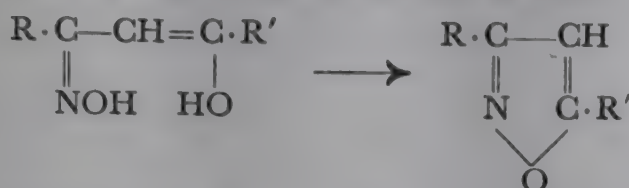
The oxazoles are weak bases, frequently with a pyridine-like odour, which often give well-crystallized picrates or double salts with platinum chloride. They are decomposed on boiling with acids. This is true especially of the 2-alkyl-(or aryl-) 5-alkoxyoxazoles, which are formed by the action of phosphorus pentachloride on acylated amino-acid esters, and which, being simple anhydrides of the latter, have attained some importance in recent times in constitutional problems in protein chemistry:



For the same reason the *oxazoline derivatives* (dihydrooxazoles) are of importance. They have been studied by M. Bergmann. Thus, N-benzoylserine methyl ester undergoes anhydridization and ring closure to the ester of 2-phenyloxazoline-4-carboxylic acid when treated with thionyl chloride. Whilst these oxazoline rings are very stable towards alkalis, they suffer hydrolytic cleavage to *o*-acylaminoacids even in weakly acidic solutions:



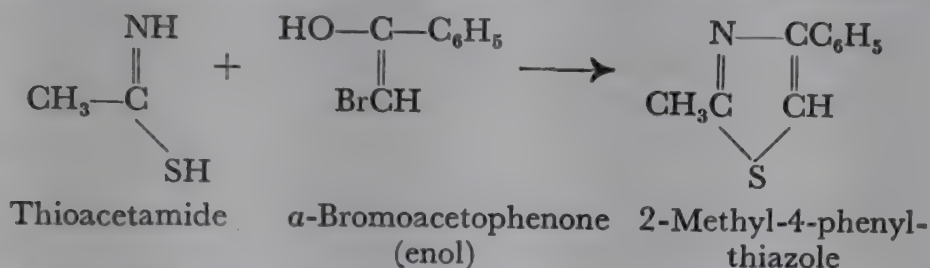
The *isoxazoles* are of little interest. They are formed, for instance, from the monoximes of β -diketones and β -ketonic aldehydes by elimination of water:



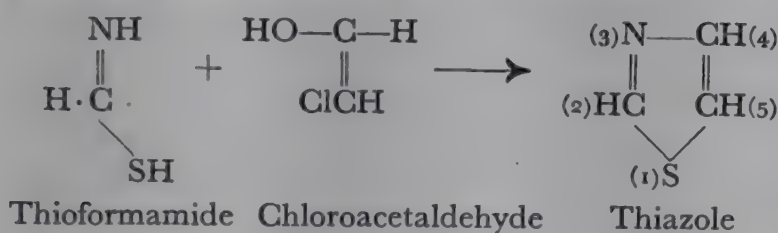
They are weak bases, and frequently have a pyridine-like smell.

Thiazole derivatives. Thiazole compounds are readily obtained by various synthetic methods, which have been worked out largely by Hantzsch. Thus they are formed:

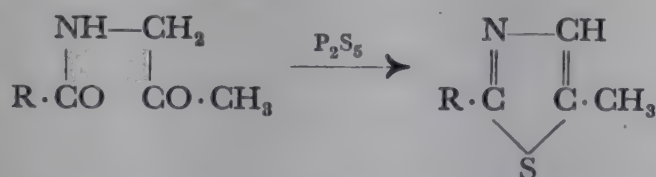
(a) From thioamides and α -halogenated aldehydes or ketones:



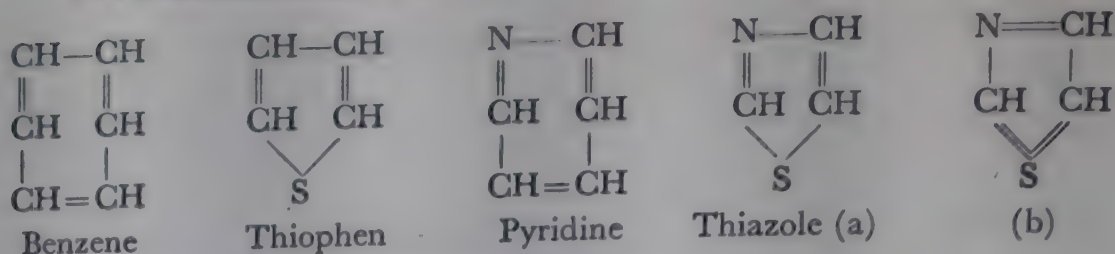
Thiazole itself has also been obtained by this method:



(b) From acylated amino-aldehydes, amino-ketones, and amino-acid esters by means of phosphorus pentasulphide:

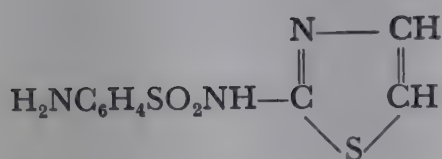
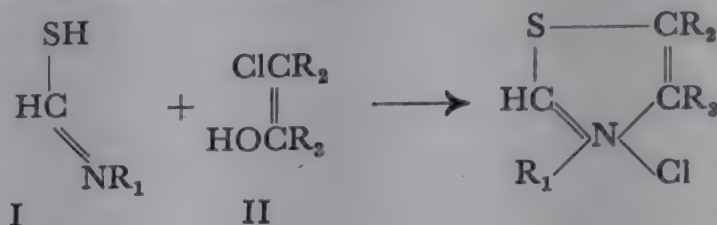


The thiazoles are distinguished by very great stability. They are hardly attacked at all by nitric acid even when hot. They are unaffected by reducing agents. Their aqueous solutions react neutral, and with acids they form stable salts, which have an acid reaction. The behaviour of the thiazoles strongly recalls that of the pyridine compounds, to which they are similar in smell, and with which they almost agree in many physical constants (b.p. of thiazole, 117° (corr.); that of pyridine, 115°). Between these two groups of compounds there exists an analogy similar to that between benzene and thiophen derivatives, and the constitutional difference is the same in both pairs of compounds (replacement of $-\text{CH}=\text{CH}-$ by $-\text{S}-$).

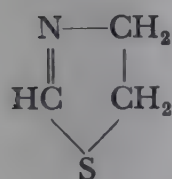


It appears that thiazole can also react in the mesomeric form (b).

Thiazol'inium salts, of which vitamin B₁ is an example, can be obtained by the condensation of N-substituted thioformamides (I) with α -halogenated ketones (II). The former can be obtained from dithioformic acid (potassium salt) and amines (Todd):



2-(*p*-Aminobenzenesulphonamido)-thiazole is successfully used to combat gonococcal, pneumococcal, meningococcal and other infectious diseases ("Sulphathiazole", "Cibazole") (see also pp. 466 and 808).

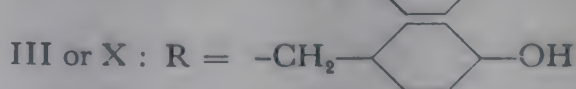
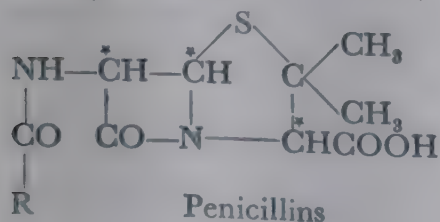


Thiazoline and its derivatives offer little new. They are stronger bases than the thiazoles.

The dyes *dehydro-thio-p-toluidine* and *primuline*, which have been described elsewhere (p. 630), belong to the compounds with multinuclear condensed thiazole systems.

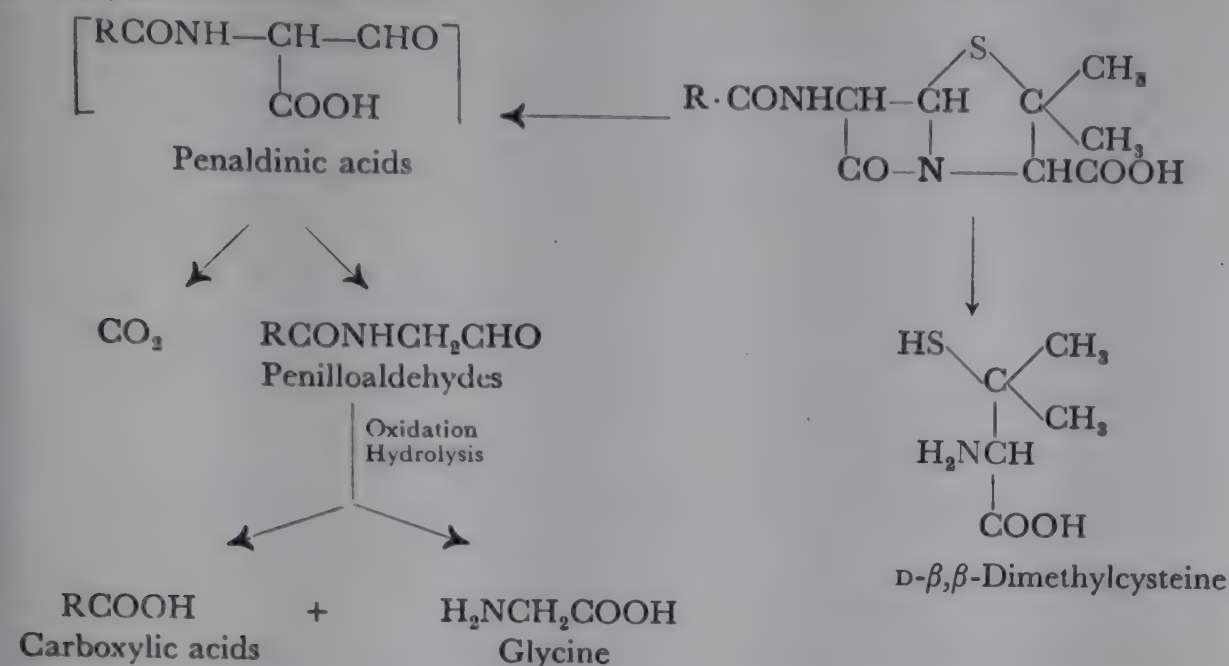
Penicillins. The *penicillins*, occurring in various moulds, especially *Penicillium notatum*, have been the object of intensive investigations, as they have proved most active as antibiotics in the treatment of many infections, and have, therefore, attained considerable therapeutic importance. A great many biologists and chemists have participated in their discovery and investigation, among whom A. Fleming, H. W. Florey, E. B. Chain, R. Robinson, and V. du Vigneaud may be mentioned.

The 4 known penicillins are unstable compounds of complicated structure, having the general formula I and containing in their molecules a thiazolidine ring, for which reason they will be discussed here. They differ in the nature of the residue R, which, in penicillin I or F, is the Δ^2 -pentenyl residue; in penicillin II or G, the benzyl; in penicillin III or X, the *p*-hydroxybenzyl; in penicillin K (incorrectly termed IV), the heptyl; and in dihydropenicillin I or F, the *n*-amyl residue:

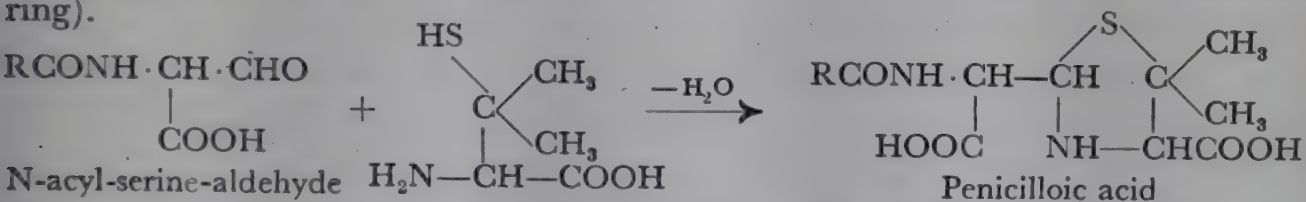


The penicillins may be decomposed by hot, dilute mineral acids into *penicillamine* and unstable "penaldic acids". The former proved to be D- β , β -dimethyl-

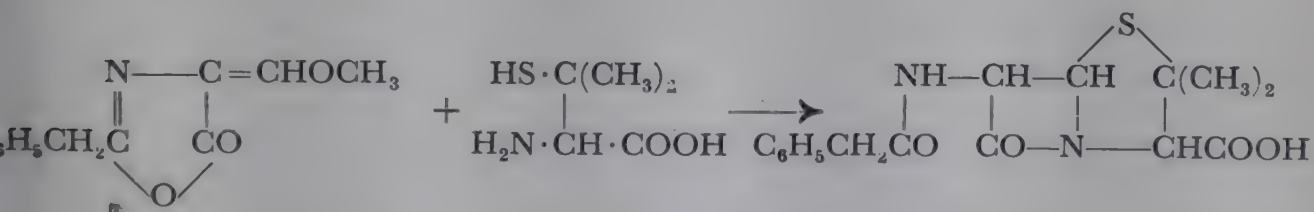
cysteine, and has been synthesized. The penaldic acids decompose further into CO_2 , and *penilloaldehydes*, which, after oxidation, are degraded to glycine and carboxylic acids RCOOH :



The penicillins may be regarded as being derived from D- β,β -dimethylcysteine and N-acyl derivatives of a serine-aldehyde, which have combined to form thio-amino-acetals or penicilloic acids, followed by dehydration to the β -lactam. The penicilloic acids are obtained from the penicillins by the action either of alkali or of an enzyme, penicillinase (hydrolytic fission of the β -lactam ring).

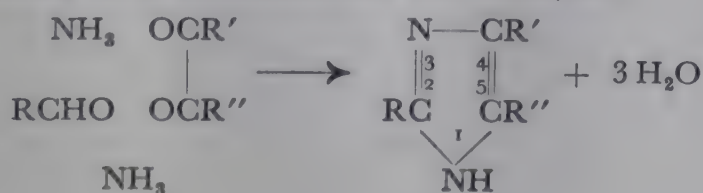


The *synthesis* of penicillin has been accomplished by the action of 2-benzyl-4-methoxymethylene-oxazolone on penicillamine; the yield was, however, extremely small:



Imidazole (glyoxaline) and its derivatives. The ring system present in imidazole is analogous to that in oxazole and thiazole, but contains the imino-group, $-\text{NH}-$, in place of oxygen or sulphur. It is the parent substance of various natural substances, and a large number of synthetic compounds.

A general synthesis for imidazole derivatives is the condensation of 1:2-dicarbonyl compounds with ammonia and an aldehyde:



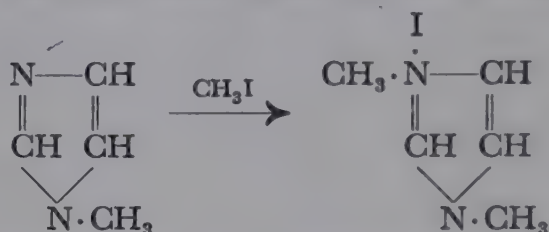
If glyoxal, formaldehyde, and ammonia are used, *imidazole* itself is formed. The alternative name for the compound, *glyoxaline*, is derived from the fact that it is obtainable from glyoxal by this reaction.

The imidazoles differ considerably from the pyrroles by virtue their greater basicity. They are monacid bases, and with mineral acids form salts which are stable towards water. On the other hand, those compounds which are not substituted on nitrogen possess, to some extent, acidic properties also, a potassium-imidazole being known, in which potassium is linked with the nitrogen in place of hydrogen.

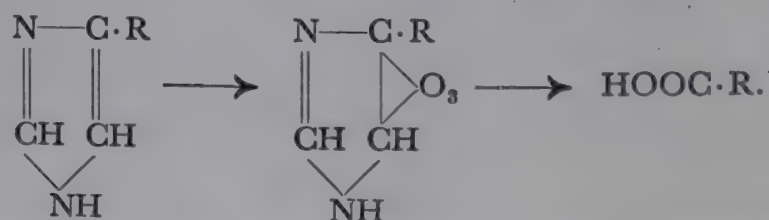
Imidazole and potassiumimidazole react with alkyl halides with the formation of N-alkylimidazoles. If these are passed through a red-hot tube, they undergo isomerization to 2-alkylimidazoles:



The N-alkylimidazoles can be further alkylated to quaternary salts. The addition of alkyl halide always takes place at the nitrogen atom not already alkylated:

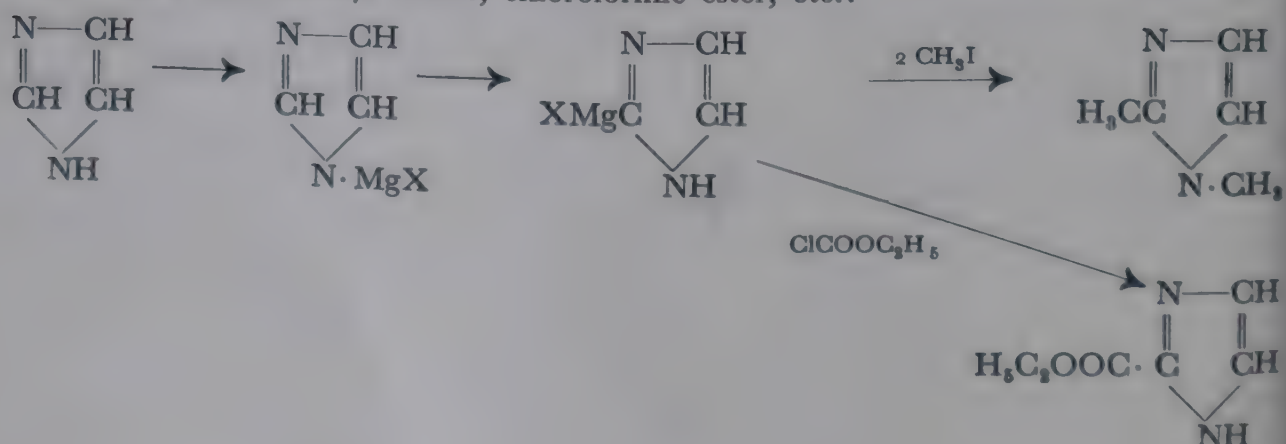


Reducing agents do not attack the glyoxalines. Among oxidizing agents, chromic acid is without action, potassium permanganate leads to complete disruption, and ozone causes fission at the C-double bond:



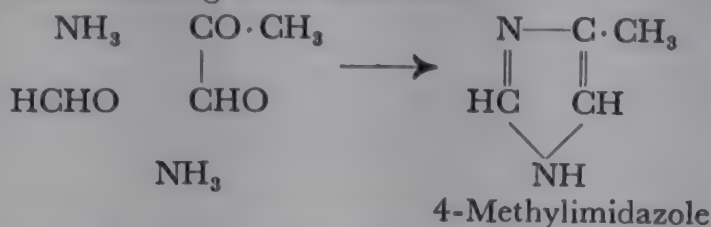
Halogens substitute successively all three of the hydrogen atoms attached to carbon in imidazole.

By the action of $\text{C}_2\text{H}_5\text{MgBr}$ on imidazole, imidazolemagnesium bromide is produced, and ethane is evolved. Apparently the magnesium first replaces the hydrogen atom attached to the nitrogen, and then migrates to a carbon atom. This magnesium derivative reacts readily with methyl iodide, chloroformic ester, etc.:

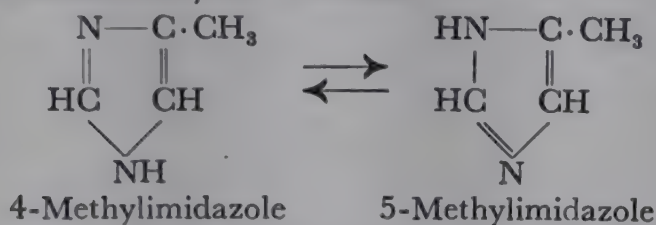


Glyoxaline melts at 90°, and boils at 256°. This remarkably high boiling point seems to be due to the marked degree of association of the imidazole, which results from the presence of the imino-group.

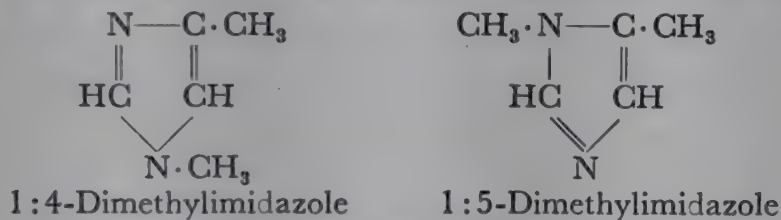
An interesting method of preparing 4-methylimidazole consists in the action of the compound of zinc hydroxide with ammonia on glucose and similar carbohydrates (Windaus). The sugar is first converted into methylglyoxal, the presence of which may be shown by precipitating it as its osazone, and formaldehyde, the two substances then reacting with ammonia:



There is, moreover, tautomeric equilibrium between 4-methylimidazole and 5-methylimidazole, and likewise between other glyoxalines substituted in the 4- or 5-position, as indicated by the formulæ:



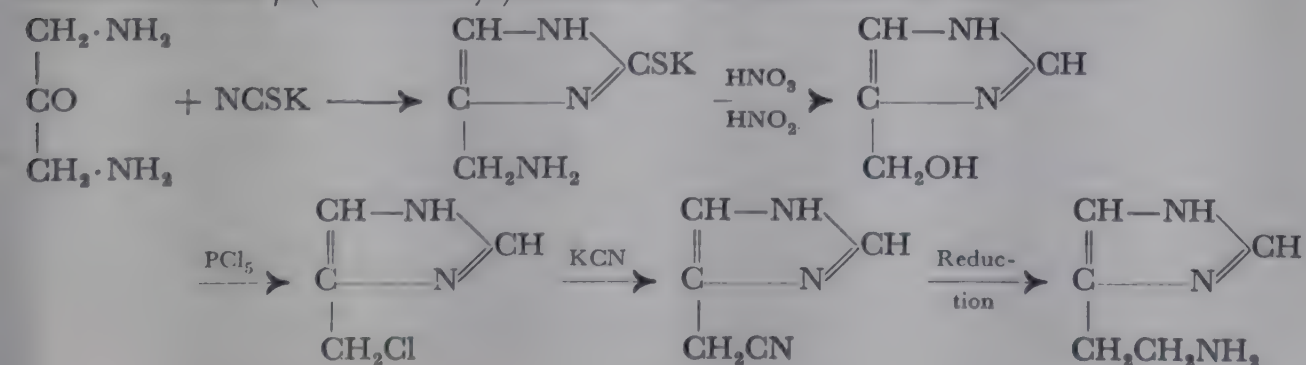
Only one compound of this formula is known, and on alkylation it behaves as a mixture of the two isomers and is converted into 1:4- and 1:5-dimethylimidazoles:



HISTIDINE. An important imidazole derivative which has already been met with as an amino-acid from proteins, is histidine (see p. 287 ff.).

On heating with mineral acids, or under the action of bacterial putrefaction, histidine is decarboxylated, *histamine*, β -(aminoethyl)-imidazole, being formed. This base reduces the blood pressure, and is used for this purpose in medicine. It has been isolated from the spleen of cattle and horses.

Histamine (m.p. 83°, b.p. 209–210°) is also obtainable synthetically. Thus, Pyman condensed diamino-acetone with potassium thiocyanate to 2-mercapto-4-aminomethylglyoxaline (other α -amino-ketones can be converted into imidazole derivatives in a corresponding way). By the action of nitric and nitrous acids on this substance 4-hydroxymethylglyoxaline is produced, which is converted into β -(aminoethyl)-imidazole *via* the chloride and nitrile:



HERCYNINE, the betaine of histidine, has been found in various fungi.

The imidazole nucleus is also found in many alkaloids, such as *pilocarpine* and its analogues (see Ch. 72), and the *purine* compounds (see p. 823).

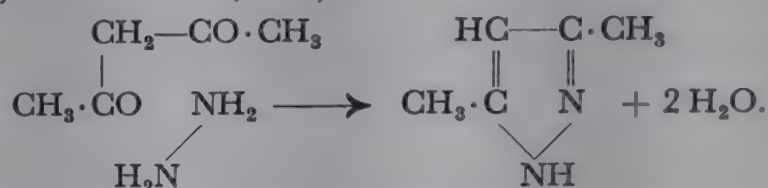
For the oxygen derivatives of imidazole, *hydantoin* (glycolylurea) and *parabanic acid* (oxalylurea) see pp. 296, 276.

Pyrazole and its derivatives. *Pyrazole* is isomeric with imidazole and differs from the latter in that its two nitrogen atoms are directly linked. The name of the substance indicates the relationship between this heterocyclic ring and pyrrole, from which pyrazole is derived by the replacement of an α -CH-group by nitrogen.

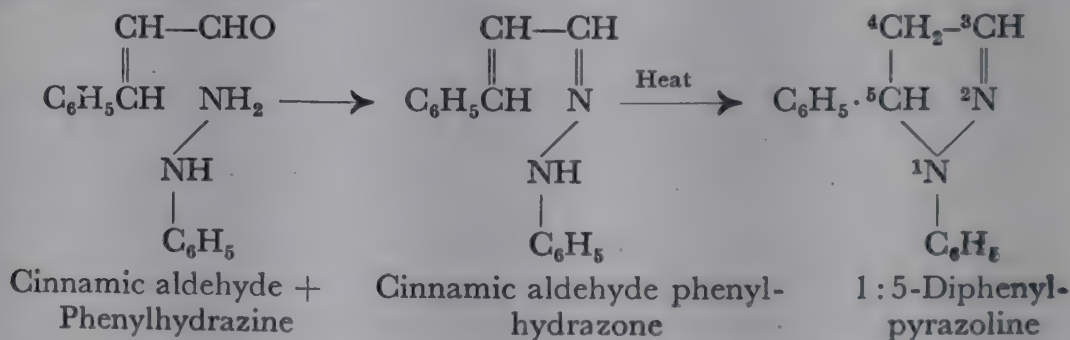
The pyrazole group has been very considerably developed and its members are obtained solely by synthesis; it is not known with certainty whether this ring system occurs in natural products.

The majority of the *syntheses of pyrazole compounds* start with hydrazine and its derivatives, or with aliphatic diazo-compounds:

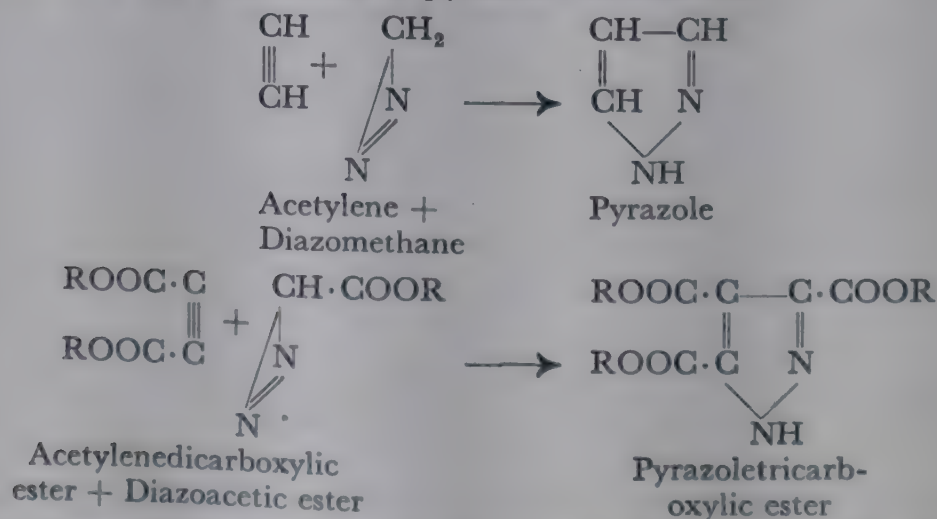
1. Hydrazine is made to react with 1:3-dicarbonyl compounds (diketones, aldehydo-ketones, ketonic acids, etc.):



2. Hydrazine or its derivatives are allowed to react with α,β -unsaturated aldehydes, ketones, or acids:



3. Diazomethane, diazoacetic ester, and the like add on to acetylenic compounds with the formation of pyrazole derivatives:

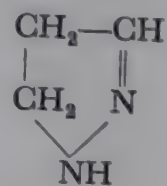


Pyrazoles are very stable compounds, which show no inclination towards resinification or polymerization. They are weakly basic. Their mineral salts dissociate even in a vacuum, and are decomposed in water.

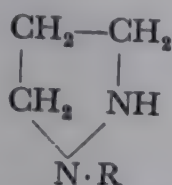
Pyrazole melts at 69–70°, has an odour of pyridine, and readily dissolves in water, alcohol, ether, and benzene. It behaves like a monacid base.

The pyrazole ring is stable towards permanganate. It is sulphonated by sulphuric acid, and nitrated by the action of nitric acid. 4-Aminopyrazole, which is prepared from 4-nitropyrazole by reduction, can be diazotized like an aromatic amine, and the diazo-compound coupled in the normal way. The aromatic character of pyrazole is thus well defined.

Pyrazole compounds can be reduced to *pyrazolines* by sodium and alcohol, but, like those of benzene, not easily. For this reason other methods are usually employed for the preparation of pyrazolines and also *pyrazolidines* (see, for example, above, method 2).



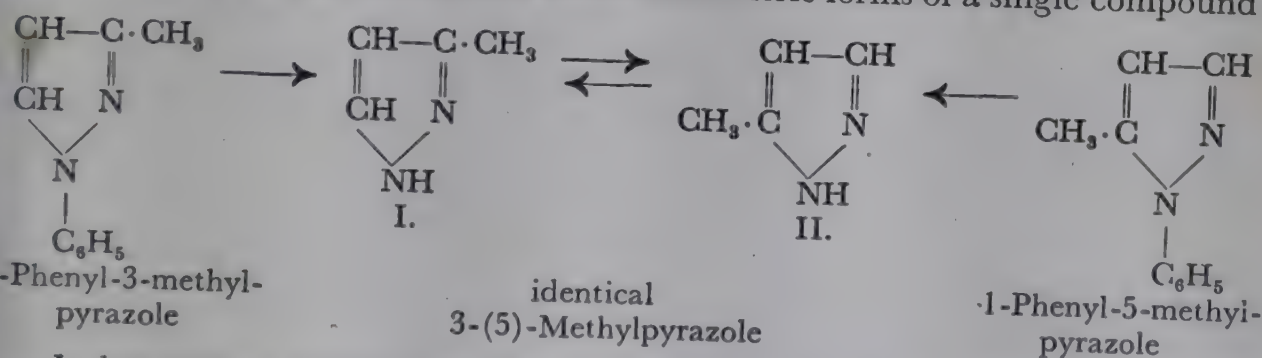
Pyrazoline



Pyrazolidine derivative

Both classes of hydrogenated compounds are stronger bases than pyrazole derivatives. Pyrazolines are also more unstable, and are readily attacked by oxidizing agents.

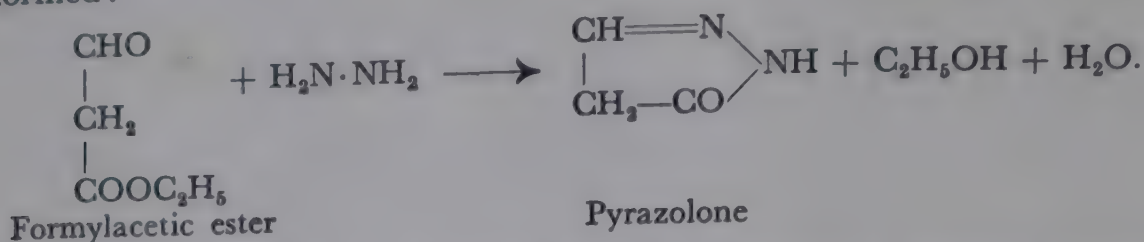
The exhaustive researches of Knorr, von Auwers, and others, have been concerned with the *constitution* of the pyrazole nucleus, and especially the distribution of the double bonds. From their work the conclusion is drawn that the double bonds of the pyrazole nucleus may change their positions according to circumstances, and, like those of benzene (see p. 378) and imidazole (see p. 793), can "oscillate". If the phenyl radical in 1-phenyl-3-methylpyrazole and 1-phenyl-5-methylpyrazole is destroyed by oxidation, the same C-methylpyrazole, which can be considered either as 3-methyl- or 5-methylpyrazole, is produced. These two formulæ (I and II) correspond to the tautomeric forms of a single compound:



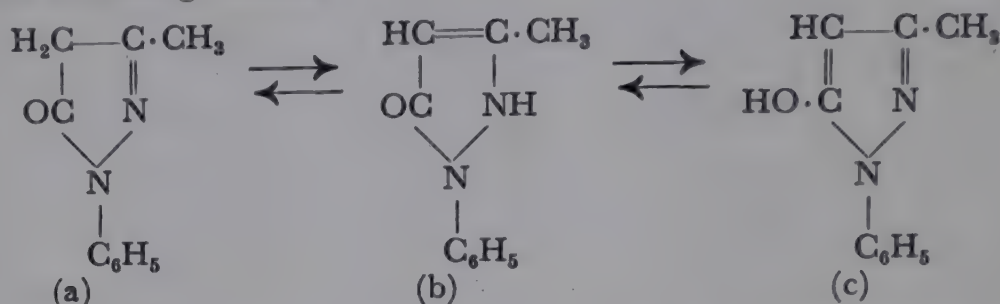
It does appear, however, that, with certain substituents at the carbon atoms of the pyrazole ring, the molecule can be stabilized to such an extent that, of the two possible tautomeric forms, one greatly predominates, so that in practice the substance can be allotted one definite structure. This holds, for example, for the methyl ester of 3-phenylpyrazole-5-carboxylic acid.

Certain keto-derivatives of pyrazoline, the *pyrazolones*, have been very extensively studied. The reason for this was the important discovery, made accidentally by Knorr, that 1-phenyl-2:3-dimethyl-5-pyrazolone (*antipyrene*) was a very useful antipyretic. The group of compounds was therefore thoroughly investigated from this point of view by Knorr and his school, as well as by industry. Later it was found that pyrazolone derivatives were also useful as dyes or in the synthesis of dyes, and to-day they form an exceedingly well-developed and important group of dyes.

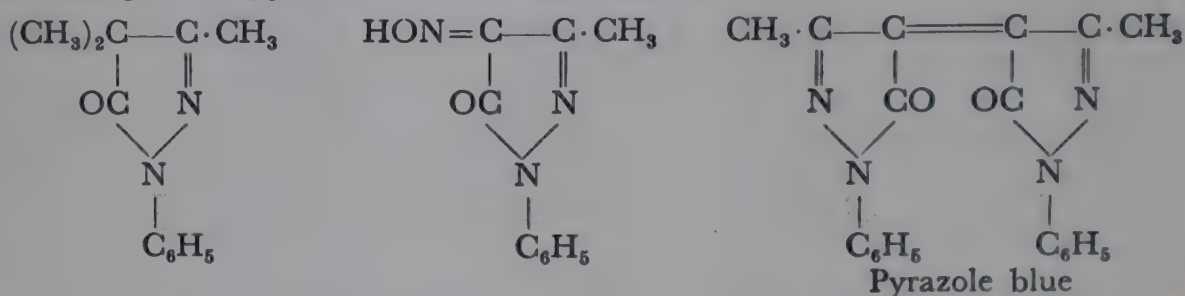
A very general *synthesis of pyrazolone compounds* consists in the action of hydrazine or hydrazine derivatives on esters of β -ketonic acids (see p. 267). If formylacetic ester is used in place of the latter, the parent substance, the simplest pyrazolone, is formed:



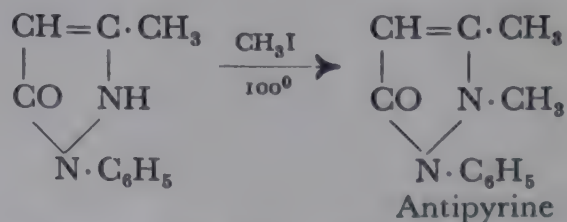
In pyrazolones, as in pyrazoles, there is a tendency towards tautomerism. Such substances (e.g. the 1-phenyl-3-methyl derivative) may react according to the three following formulæ:



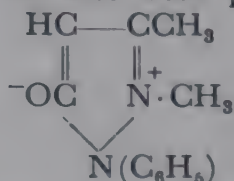
4:4-Dialkyl derivatives, *isonitroso*-compounds, as well as *Pyrazole blue*, a dye of the indogenide type, are derived from formula (a):



Antipyrine, which is obtained from 1-phenyl-3-methylpyrazolone by methylation with methyl iodide and methyl alcohol, is an example of a derivative of the second formula (b):



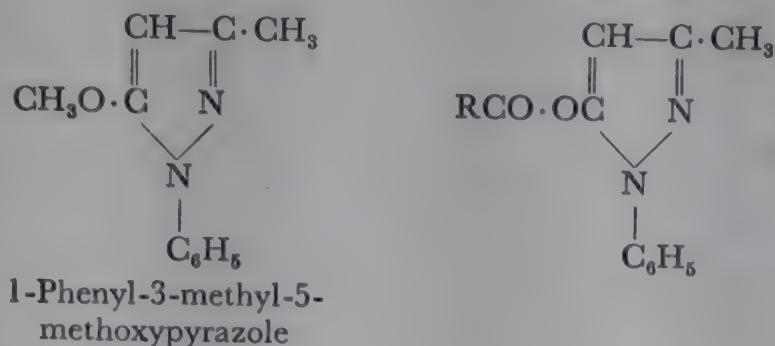
A "phenol-betaine" formula has also been put forward for this compound by Michaelis:



which, for example, explains satisfactorily the considerable solubility of antipyrine in water (salt-like character), though it appears to be less consistent with the Raman spectrum.

The third formula (c) is invoked to explain the formation of O-alkyl and O-acyl compounds of the pyrazolones. Thus, 1-phenyl-3-methylpyrazolone is converted into 1-phenyl-3-methyl-5-methoxypyrazole by diazomethane, and

into O-acyl derivatives by means of acid chlorides and alkali, thus behaving like a phenol:

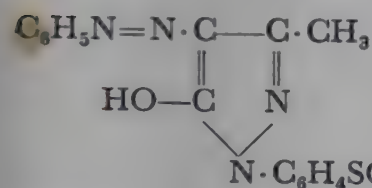


ANTIPYRINE (Knorr, 1884). The formula and method of preparation of this compound are given above. It is very soluble in water, reacts neutral, and tastes bitter. It melts at 113°. Ferric chloride gives a brownish red colour with its aqueous solution. The compound is of great importance as an antipyretic.

Nitrous acid reacts with antipyrine producing a green 4-nitroso-derivative, which can be reduced to 4-aminoantipyrine. This base behaves like an aromatic amine. It can be diazotized, and the diazo-compound can be coupled, and will enter into "Sandmeyer reactions", exchanging its diazo-group for other groups.

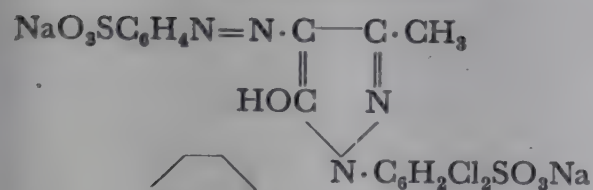
Methylation of 4-aminoantipyrine gives *pyramidone*, N-dimethylaminoantipyrine, an important substance in medicine (Stolz). It is a stronger and more lasting antipyretic than antipyrine, and possesses good anti-neuralgic properties. It melts at 108°.

PYRAZOLONE DYES. The majority of these belong to the group of azo-dyes, and are obtained by coupling diazonium salts with 1-phenyl-3-methylpyrazolone or analogous substances. On account of their excellent fastness to light they have become of considerable importance in recent years. The following representatives of this class may be mentioned:



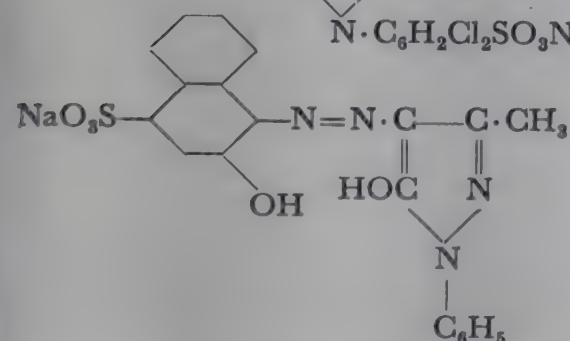
Fast light yellow G, or Flavazine.

(made from 1-*p*-sulphophenyl-3-methylpyrazolone and diazotized aniline).



Xylene yellow 3 G.

(from 1-[2:5-dichloro-4-sulphophenyl]-3-methylpyrazolone and diazotized sulphanic acid).



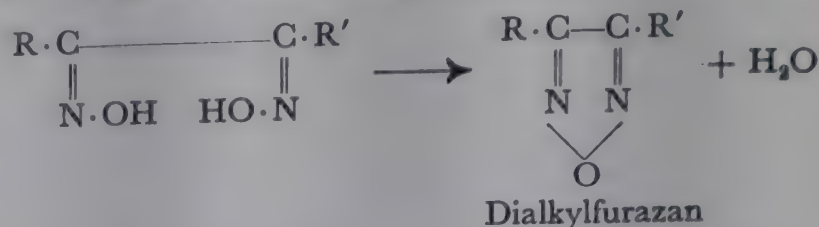
Eriochrome red B.

(from 1-phenyl-3-methylpyrazolone and diazotized 1-amino-2-naphthol-4-sulphonic acid).

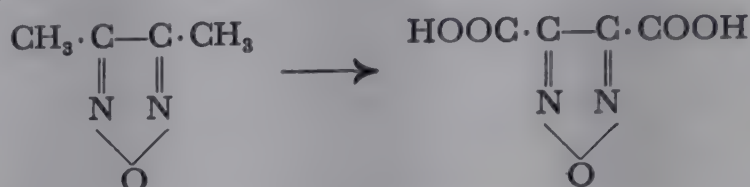
The pyrazolone dye tartrazine is dealt with on p. 490.

B. Five-membered heterocyclic rings with three or more hetero-atoms

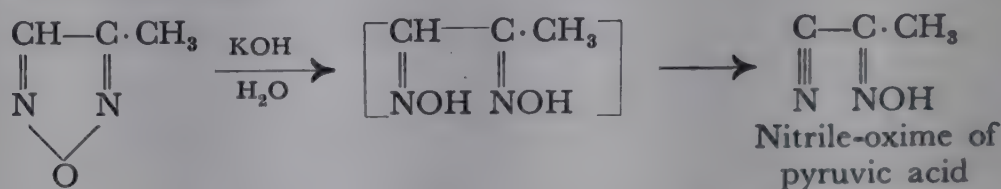
Furazans. Furazans can be regarded as anhydrides of the α -dioximes, from which they are indeed formed by the elimination of water (e.g. on heating with ammonia):



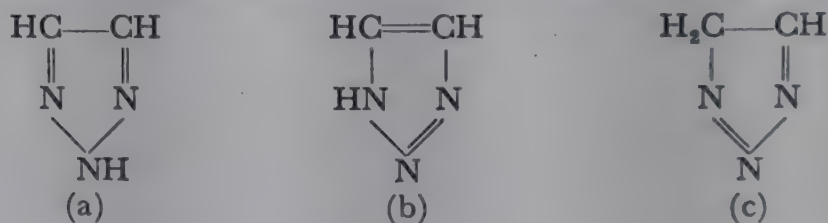
The disubstituted furazan ring is distinguished by its great stability. Even by oxidation with potassium permanganate the ring is not ruptured, the effect of the oxidizing agent being limited to the break-down of the side chains. In this way, dimethylfurazan gives the dicarboxylic acid:



Monoalkylated furazans undergo rupture more readily. Alkalis convert them into nitrile-oximes of ketonic acids:

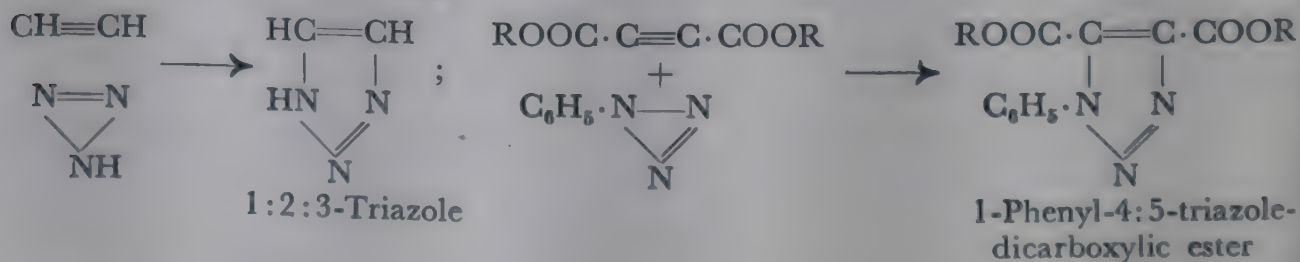


1:2:3-Triazoles. Three tautomeric formulæ can be assigned to 1:2:3-triazole:

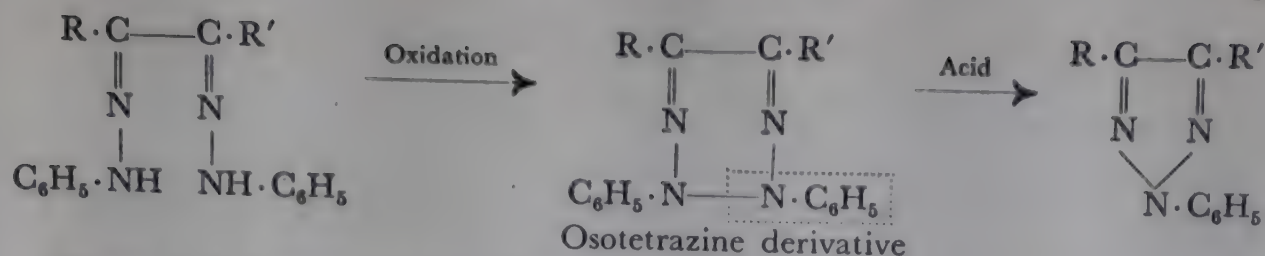


At present only derivatives of the parent compound which are derived from the formulæ (a) and (b) are known.

There are many methods for preparing 1:2:3-triazole compounds. First may be mentioned the action of hydrazoic acid or its organic derivatives, the azides, on acetylenic substances:

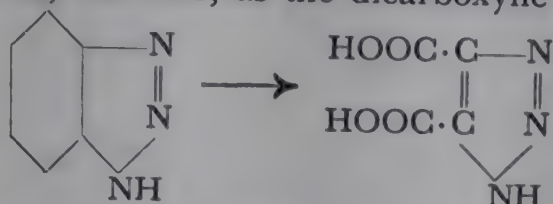


A second method for the preparation of 1:2:3-triazoles starts from the phenyl-osazones of 1:2-dicarbonyl compounds. Their oxidation products, the *osotetrazines*, undergo ring contraction when boiled with acids, and are converted into triazole derivatives with elimination of the $\text{C}_6\text{H}_5\text{N}-$ group:



Those 1:2:3-triazoles in which the heterocyclic nucleus is condensed in the *ortho*-position with a benzene nucleus, the *azoimides*, have been known longest. They are obtained from aromatic *ortho*-diamines by the action of nitrous acid (see p. 458).

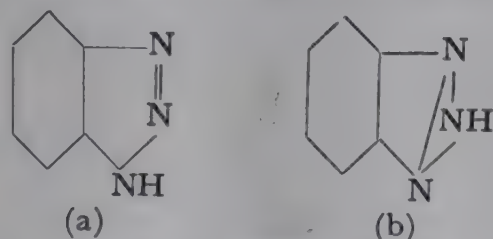
By powerful oxidation the aromatic nucleus of the azoimides is destroyed. The triazole half remains, however, as the dicarboxylic acid:



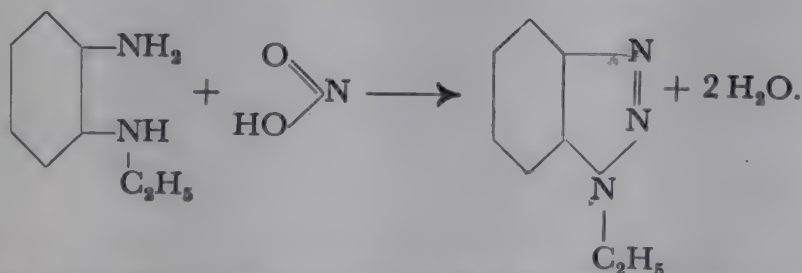
It may be concluded from this that the ring system of the 1:2:3-triazoles is very stable, and this is confirmed by the other properties of these compounds. Only towards reducing agents are they more sensitive. The triazoles are very weak bases. The hydrogen atom attached to the nitrogen can be replaced by a metal (it is thus "acidic"). The C-amino-derivatives are capable of being diazotized. A marked relationship with the aromatic substances is thus found also with these heterocyclic bases.

1:2:3-Triazole boils at 203° (239 mm) and melts at 23°. It has a weakly amine-like smell. It forms metal salts (e.g. with silver, mercury, etc.) as well as salts with mineral acids. The latter are hydrolysed in water.

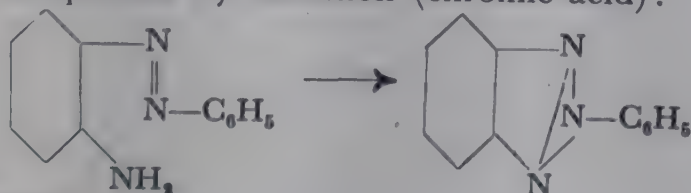
Aziminobenzene, *benzotriazole*, can exist, theoretically, in two tautomeric forms:



Derivatives of both are known. Those derived from (a) are formed in a straightforward way from aromatic N-monoalkyl- (or aryl-) *o*-diamines and nitrous acid:

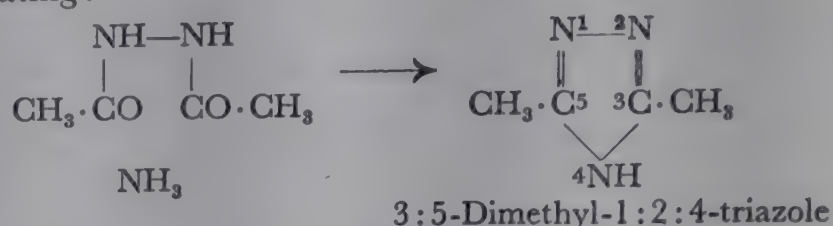


Derivatives of the tautomeric form (b) of the parent substance can be obtained from *o*-aminoazo-compounds by oxidation (chromic acid):

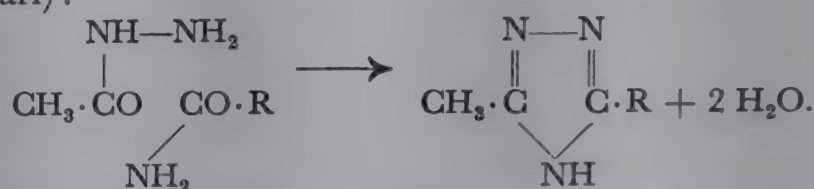


Benzo-1:2:3-triazole (aziminobenzene), whose constitution is probably given by formula (a), above, is a well-crystallized, colourless compound, which, judging by the results of molecular weight determinations, is strongly associated; m.p. 100°. Aziminotoluene melts at 83–84°. Like the other azoimides they are very stable towards acids and alkalis, and towards oxidation and reduction. Their basic character is extraordinarily weak. On the other hand, they form stable metal salts.

1:2:4-Triazoles (1:3:4-triazoles). Hydrazine derivatives are usually employed in the preparation of these compounds. Thus, they are obtained by the action of the compound of ammonia with zinc chloride, or of amines on diacylhydrazines on heating:

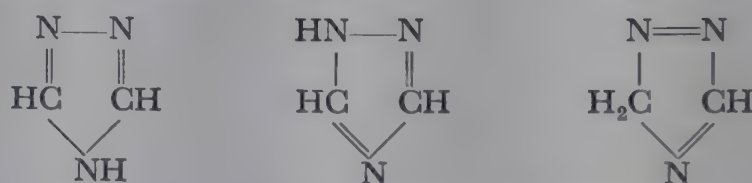


They are also obtained from monoacylhydrazines by condensation with acid amides (Pellizzari):

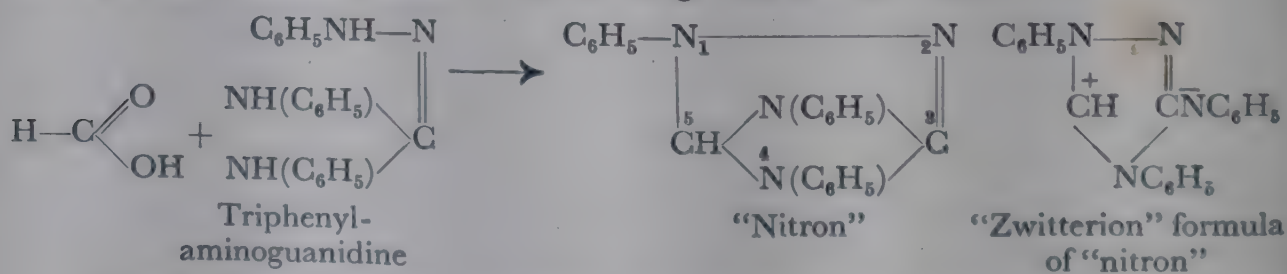


The 1:2:4-triazoles resemble the 1:2:3-triazoles in their great stability and their aromatic behaviour. Strong oxidizing agents attack the side chains of the triazole nucleus, but do not disrupt the heterocyclic ring. The 1:2:4-triazoles are also very weak bases; those which contain an unsubstituted NH-group form metal salts.

The parent substance, 1:2:4-triazole, is a colourless, odourless, crystalline compound. M.p. 120–121°; b.p. 260°. Like the isomeric 1:2:3-compound it can be written in three tautomeric forms:



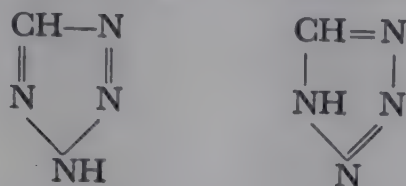
Amongst the group of 1:2:4-triazole compounds, which has been well investigated, is a compound of rather complex structure which is used in analytical chemistry under the name “nitron” for the estimation of nitrate ions. It is formed from triphenyl-aminoguanidine by heating with formic acid:



In the final product of the reaction, a phenylated nitrogen bridge extends from position 3 to position 5 of the triazole nucleus. Such compounds are called

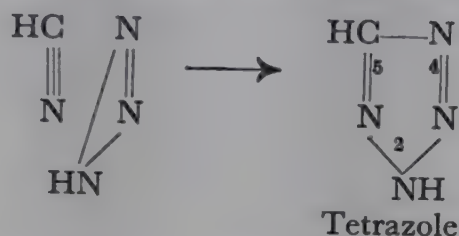
"endoimino" compounds, and the above-mentioned nitron itself may be called *1:4-diphenyl-endoanilo-dihydrotriazole* or *1:4-diphenyl-endoanilo-triazoline* (briefly, *1:4-diphenyl-danilo-dihydrotriazole*). It forms yellow leaflets, melting at 189°. Its acetate is readily soluble in water, but the nitrate is practically insoluble. Upon this fact is based the use of nitron for the quantitative estimation of the nitrate ion, which is carried out in acetic acid solution.

Tetrazole. Tetrazole possesses a ring which contains four nitrogen atoms and one carbon atom. It reacts according to the tautomeric formulæ:

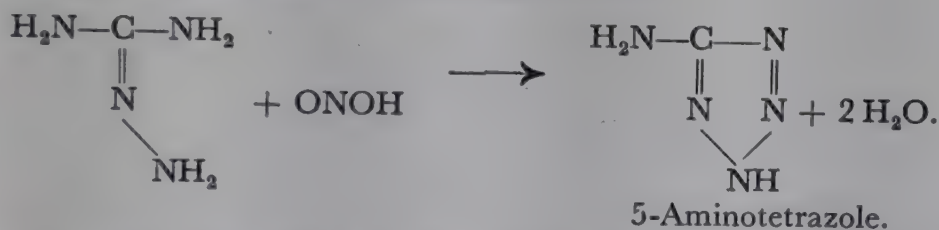


N-Alkyl and N-aryl derivatives of both forms are known.

A large number of reactions are suitable for the preparation of tetrazole compounds. The parent substance, tetrazole itself, is, for example, formed on prolonged heating of a mixture of hydrazoic acid and anhydrous hydrocyanic acid:



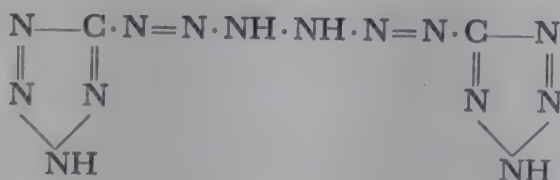
The action of nitrous acid on aminoguanidine:



as well as other reactions, gives the well-investigated 5-aminotetrazole.

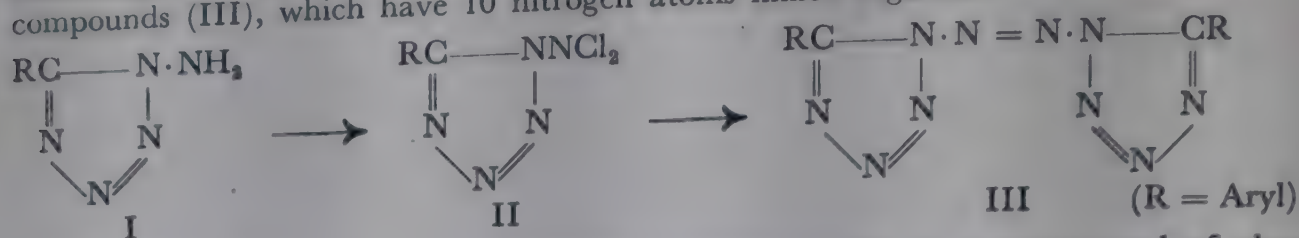
Tetrazole (m.p. 155°; colourless crystals) and its derivatives not substituted on nitrogen have an acid reaction in water, and give stable metal salts (e.g. the silver salt, and alkali-metal salts). Most tetrazole compounds are remarkably stable. Their aromatic nature is, for instance, revealed in the ability of 5-aminotetrazole to undergo diazotization in the normal way. This diazonium salt can be coupled, and enters into most of the reactions characteristic of diazonium salts, being reduced, for example, to 5-hydrazinotetrazole.

A product obtained by diazotizing 5-aminotetrazole and coupling with hydrazine, deserves mention on account of its extraordinarily high nitrogen content:



In addition to 10.7 % carbon, it contains no less than 87.5 % nitrogen, and is of all known organic compounds the richest in nitrogen.

1-AMINOTETRAZOLE DERIVATIVES (I) are also known; with HOCl they give the exceedingly explosive dichloro-derivatives (II) which are converted by KI into the azo-compounds (III), which have 10 nitrogen atoms linked together:

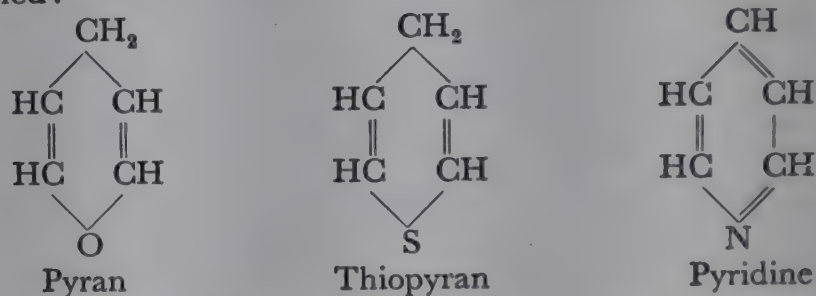


Pentamethylenetetrazole is a compound of pharmacological interest. It is a stimulant, and is used under the names *leptazole* or *cardiazole*, as a water-soluble substitute for camphor.

CHAPTER 61

SIX-MEMBERED HETEROCYCLIC RINGS WITH ONE HETERO-ATOM

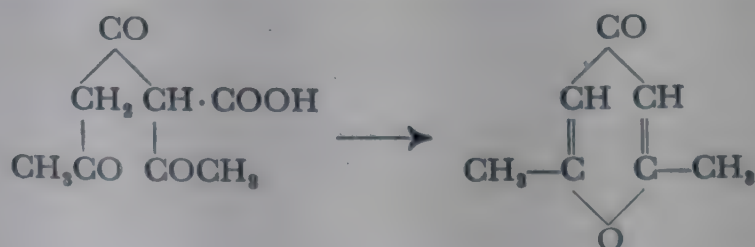
By replacement of a CH-group in the six-membered benzene nucleus by a hetero-atom, such as oxygen, sulphur, or nitrogen, ring systems of the following kind are obtained:



Of these, *pyran* and *thiopyran* are known at present only as their derivatives. The most important of them, the pyrones, xanthenes and pyrylium dyes (anthocyanins), have already been met with in earlier chapters, where they have been dealt with because of their relationships with purely aromatic compounds. Here we shall be chiefly concerned with *pyridine* and its numerous derivatives. We shall precede this, however, with a consideration of some simple pyran compounds, as they give some interesting information on the valency distribution in this ring system.

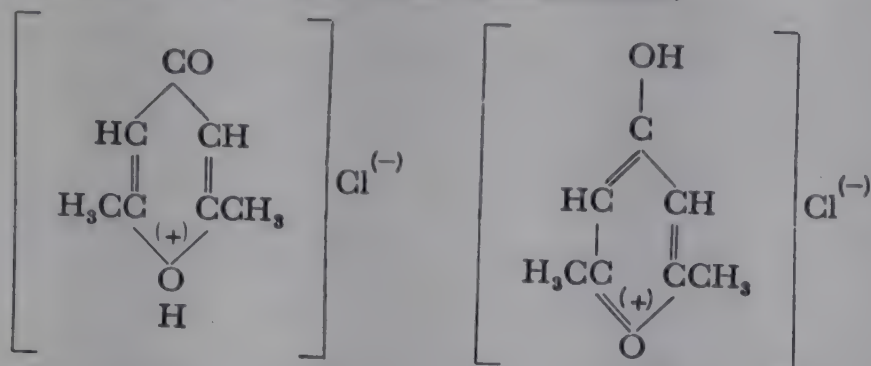
Pyran derivatives

One of the best investigated of the simple pyran derivatives is 2:6-dimethyl- γ -pyrone, which can be obtained synthetically in several ways, for example, by boiling "dehydracetic acid" (α,γ -diacetyl-acetoacetic acid) with hydrochloric acid:

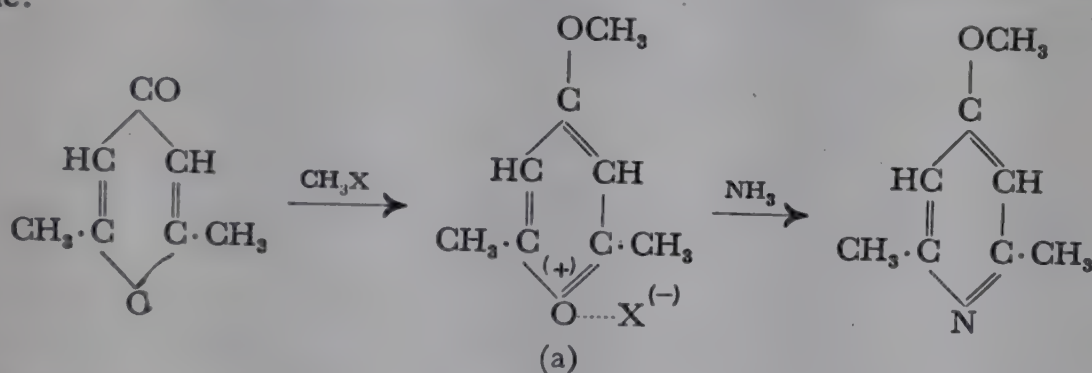


On account of its ability to form well-crystallized salts with acids, it attracted attention some fifty years ago (Collie and Tickle). It can be taken as the prototype of that numerous class of oxygen compounds in which the oxygen has basic properties, and which are capable of forming "oxonium" salts.

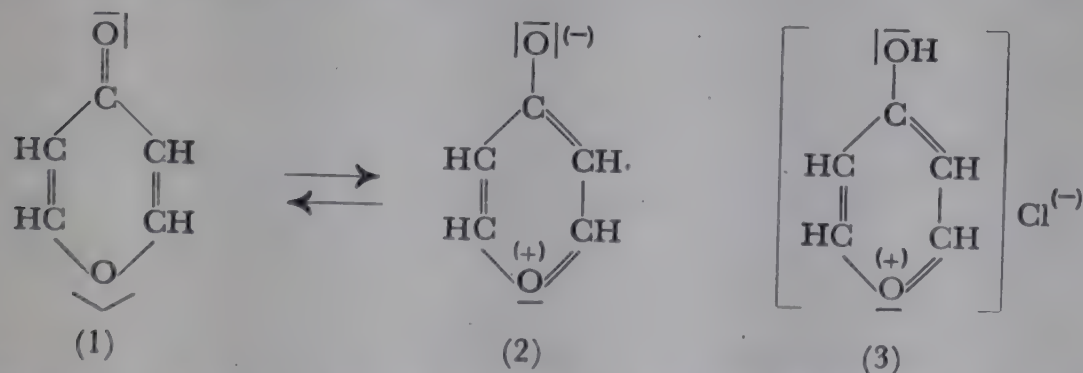
It has been shown on p. 117 that the oxygen in oxonium salts is to be regarded as coordinately trivalent. For the salts of 2:6-dimethylpyrone there are only the two following formulæ which merit serious consideration:



Of these the second appears to be the more probable. Thus, alkylating agents (dimethyl sulphate, methyl iodide) add on to dimethylpyrone (Kehrmann) with production of salts of a strong base which may be compared with the quaternary ammonium salts. Their reaction with ammonia is important in deciding their constitution. 2:6-Dimethyl-4-methoxypyridine is formed smoothly (v. Baeyer). Hence formula (a) must represent the constitution of the salts of the methylated pyrone:



The actual state of γ -pyrone, on the basis of the electronic theory, is intermediate between the limiting forms (1) and (2):

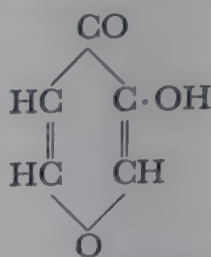
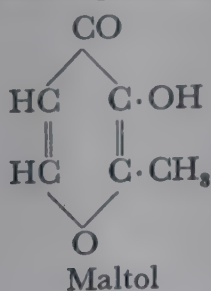


The molecules of form (2) are dipolar and will add on acids so that the proton becomes linked to the negative pole. In this way formula (3) is obtained for the hydrochloride which corresponds to the ordinary structural formula given above.

2:6-DIMETHYLPYRONE melts at 131° , and boils at 248° (713 mm). It dissolves readily in water with a neutral reaction. Its salts with mineral acids, however, give a strong acid reaction in aqueous solution owing to hydrolysis. The tendency

to form addition compounds extends in the case of these pyrone compounds to many mineral salts (e.g. HgCl_2 , CuCl_2 , ZnCl_2 , CoCl_2 , etc.), with which well-crystallized compounds are formed.

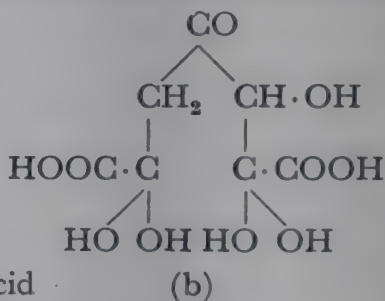
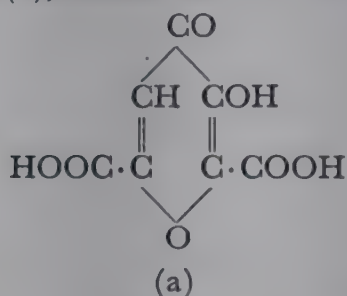
MALTOL is the name given to a simple pyrone derivative, 2-methyl-3-hydroxypyrone, which has been repeatedly found in nature:



Pyromeconic acid (3-hydroxypyrone)

It is present in pine-needles, and in the bark of larch trees, and is produced in small quantities by the dry distillation of wood and cellulose, by roasting malt, etc. It gives a characteristic violet colour with ferric chloride (adjacent carbonyl and acid hydroxyl groups!). It melts at 160° .

PYROMECONIC ACID is the lower homologue of maltol and is obtained by distillation of *meconic acid*. Meconic acid occurs in opium. In addition to the cyclic formula (a) an open chain formula (b), which stands for its trihydrate, comes also into consideration:

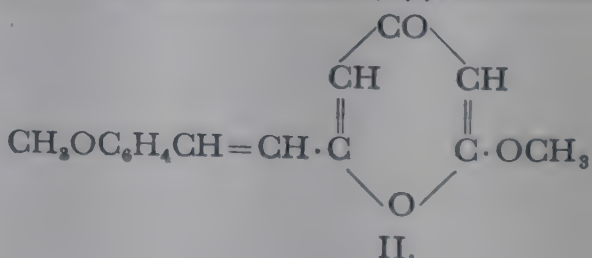
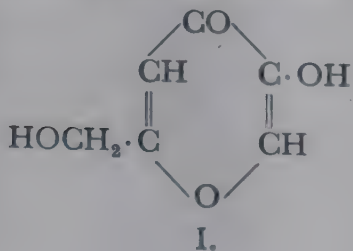


Meconic acid

The acid gives a deep red colour with ferric chloride.

By cultivating various bacteria on solutions of carbohydrates (e.g. glucose, maltose, cane sugar, fructose, inulin, and also dulcitol, glycerol, etc.), the so-called *kojic acid* (I), a simple γ -pyrone derivative, is formed. It can also be prepared by a purely chemical method from glucose.

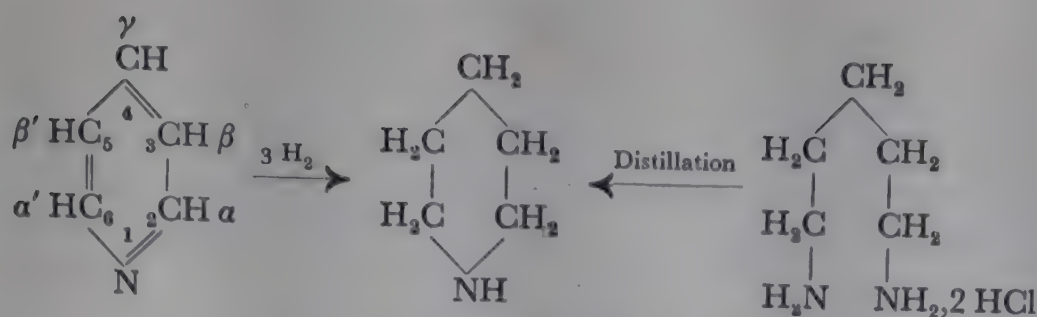
YANGONIN from the kava root has also been recognized as a γ -pyrone derivative (II):



Pyridine and its derivatives¹

PYRIDINE is a weak tertiary base, whose molecule contains five CH-groups and a nitrogen atom arranged in a six-membered ring. The constitution of pyridine follows from the fact that it is readily reduced, with the addition of six atoms of hydrogen, to piperidine, which can be obtained by a straightforward reaction from pentamethylenediamine (by distillation of its hydrochloride):

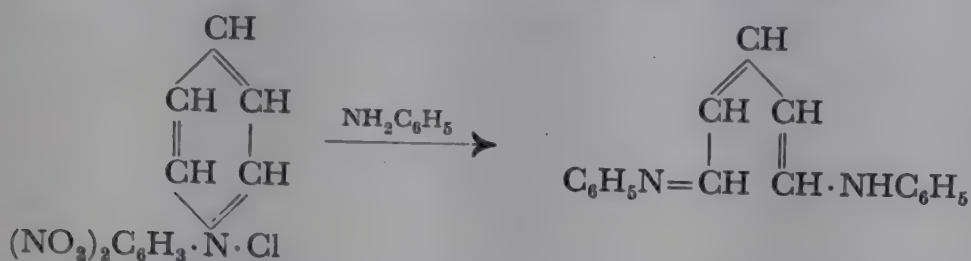
¹ See HANS MAIER-BODE and JULIUS ALTPETER, *Das Pyridin und seine Derivate in Wissenschaft und Technik*, Halle, (1934).



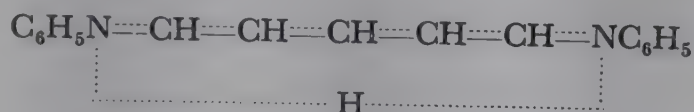
Moreover, the fission of the pyridine ring to simple aliphatic compounds supports this formula. Thus, when the addition product of dinitrochlorobenzene and pyridine is treated with aniline, the anilide of glutaconic aldehyde,



a so-called polymethine dye, is formed by an unusual reaction:



In these "*polymethine dyes*" there appears to be an oscillating system of heteropolar linkages, as shown in the formula:



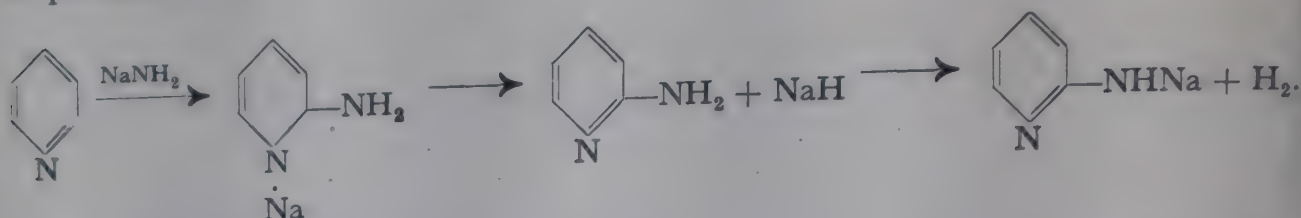
If optically active groups (*d*- and *l*-) are introduced in place of the C_6H_5 -radicals, inactive meso-forms are produced. If the two groups are different, and their places are interchanged, the same product results (W. König).

Pyridine was discovered by Anderson (1849) in bone-tar, obtained by distilling bones, in which it occurs along with higher homologues and various pyrrole derivatives. It is present in larger quantities in coal-tar, and is obtained industrially from this source.

The base is a colourless liquid, miscible with water, with a characteristic, somewhat pungent smell. It boils at 115° , and melts at -38° . It shows a definite "aromatic" character, and can be sulphonated, giving β -pyridinesulphonic acid, and nitrated under very energetic conditions (about 300°), the nitro-group also entering the β -position. β -Nitropyridine (m.p. 41°) gives β -aminopyridine on reduction, which can be diazotized in the normal way. The two other isomeric aminopyridines, the α - and γ -compounds, behave in another way with nitrous acid. In dilute mineral acid solution their diazotization is incomplete, and in a more concentrated halogen hydracid solution the diazonium salt group initially formed is replaced by halogen with evolution of nitrogen.

The relative difficulty experienced in making nitropyridines has led to the investigation of other methods of preparing the aminopyridines. They can be prepared from chloropyridines by heating with zinc chloride-ammonia, or by heating bromopyridine with ammonia and copper salts, or by the degradation of

the azides or amides of the pyridine carboxylic acids. Nowadays, however, they are often made by the direct amination of pyridine and its derivatives by heating with sodamide (Tschitschibabin). For example, 2-amino- and 2:6-diaminopyridine are formed from pyridine and sodamide. The mechanism of this reaction is probably as follows:

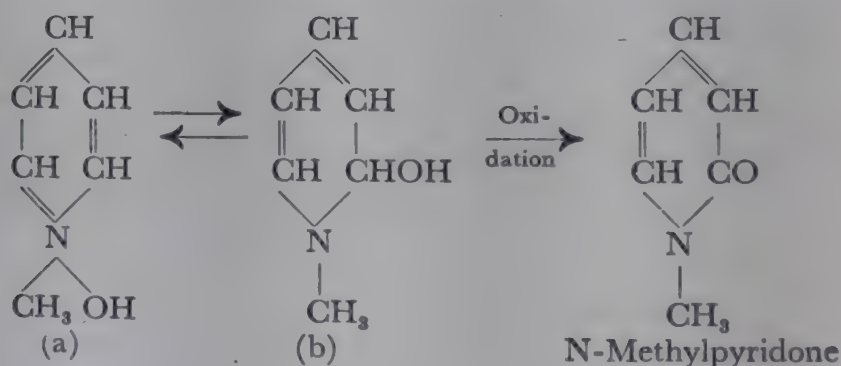


2:4-Diaminopyridine gives azo-dyes on coupling with diazonium salts, which have a powerful bactericidal action (Pyridium A). Analogous azo-dyes are also obtained from 2:6-diaminopyridine ("Pyridium" = β -benzeneazo-2:6-diaminopyridine).

2-(*p*-Aminobenzenesulphonamido)-pyridine (trade names "M. and B. 693", "Sulphapyridine", and "Dagenan") has proved to be a very effective cure for streptococcal, pneumococcal, and gonococcal diseases (see also pages 466, 792).

It should be noted that 2-bromopyridine and 2:6-dibromopyridine undergo the Grignard reaction with magnesium in the usual way.

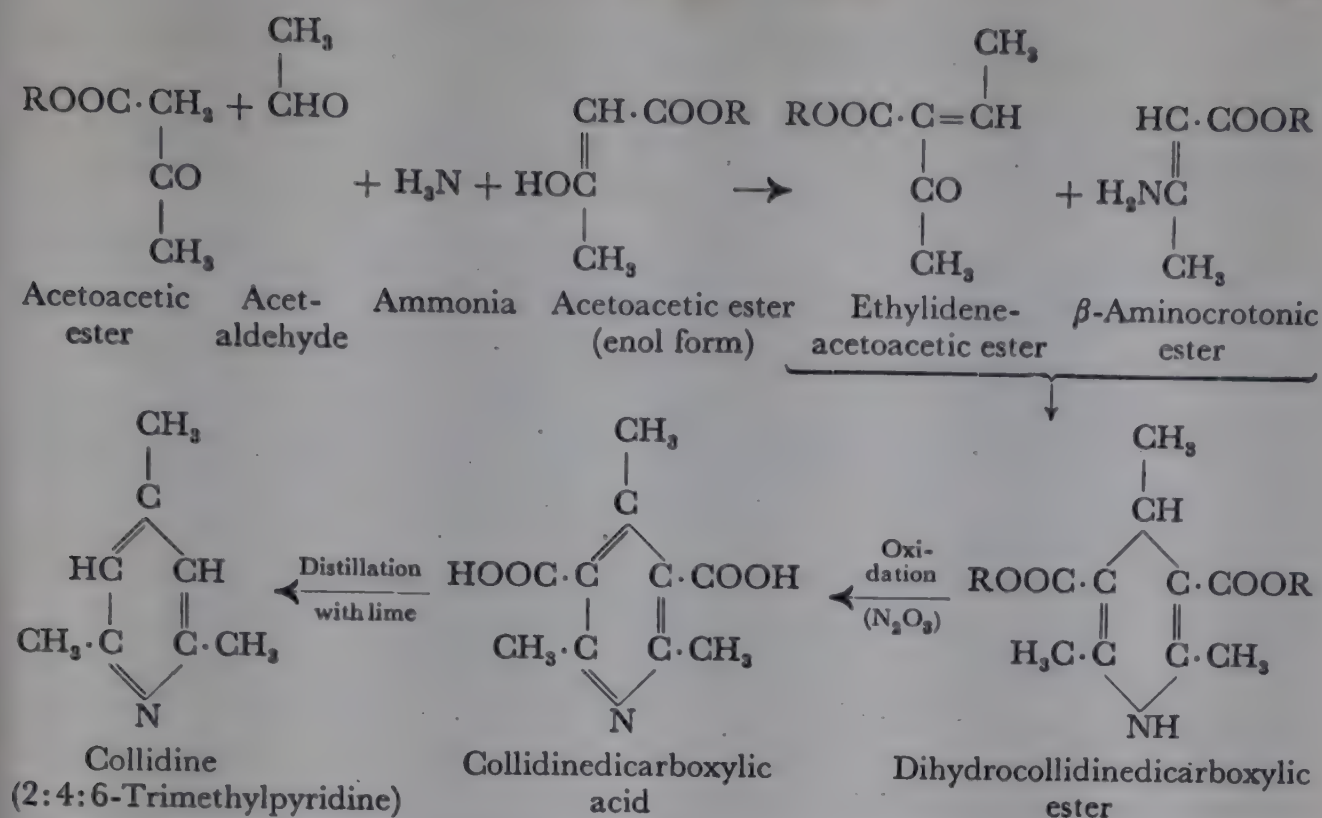
Being a tertiary amine, pyridine readily adds on alkyl halides, dialkyl sulphates, and similar alkylating agents. The quaternary pyridinium salts usually crystallize excellently. The quaternary bases corresponding to them, which are obtained by the action of alkalis, can react according to the two tautomeric formulæ given below. The existence of the carbinol form (b) is particularly supported by the fact that these bases can be oxidized by suitable oxidizing agents (potassium ferricyanide or electrolytic oxidation) to *N*-alkylpyridones (Decker):



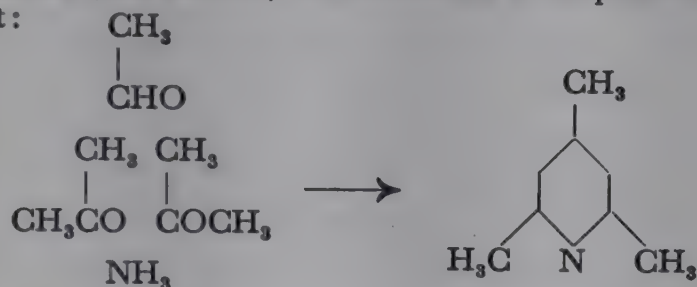
By alkylation the pyridine ring loses some of its stability and is more readily disrupted. The above-mentioned conversion into the anilide of glutamic aldehyde may be mentioned in this connection.

Pyridine plays an important part as a solvent, on account of its excellent solvent action on many inorganic salts and organic substances. In recent times it has often been used for combining with halogen hydracids liberated during acylations with acid halides. Crude pyridine is used for denaturing alcohol, and occasionally also for the extermination of plant pests.

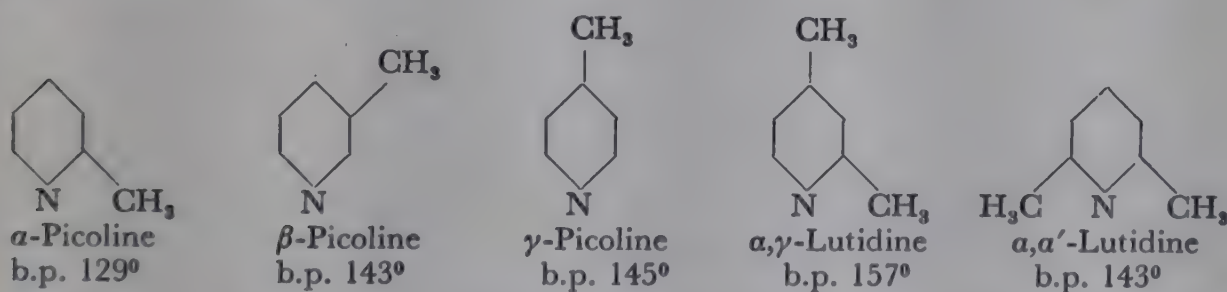
Various synthetic methods are available for the preparation of homologues of pyridine. A synthesis depending on the condensation of 2 mols. of a β -ketonic acid ester with 1 mol. of an aldehyde and 1 mol. of ammonia has proved particularly useful (Hantzsch). The mechanism of the reaction is probably as follows:



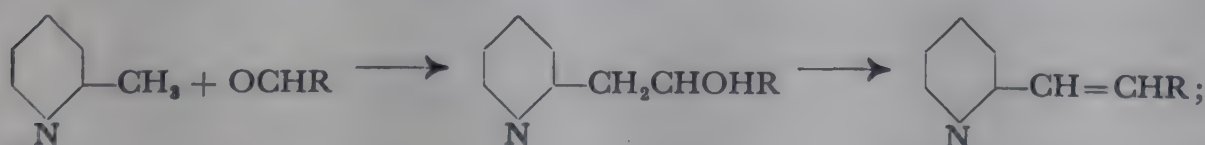
Similar in principle is the process often used by Tschitschibabin, which consists in the condensation of aldehydes (and ketones) with ammonia in the presence of aluminium oxide as a contact catalyst:

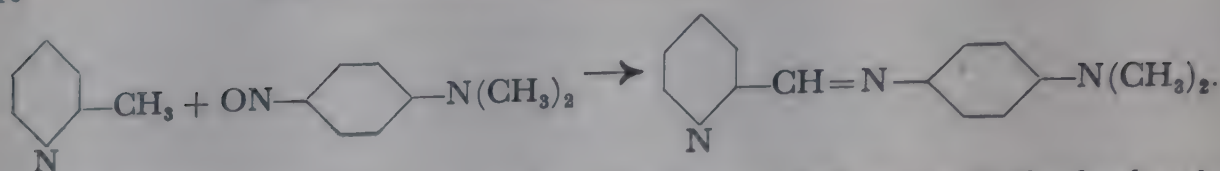


Coal-tar and bone-tar are the chief sources of mono- and dimethylpyridines, but their separation is no easy task and syntheses of the individual compounds have therefore been worked out. The mixture is used industrially for denaturing alcohol. The monomethylpyridines are known as *picolines*, and the dimethyl-compounds as *lutidines*:



The reactivity of the methyl groups in the α - and γ -positions must be emphasized. Their hydrogen atoms can react with aldehydes and nitroso-compounds, in the same way as the methylene group of acetoacetic ester. This is not the case for the β -methyl group:



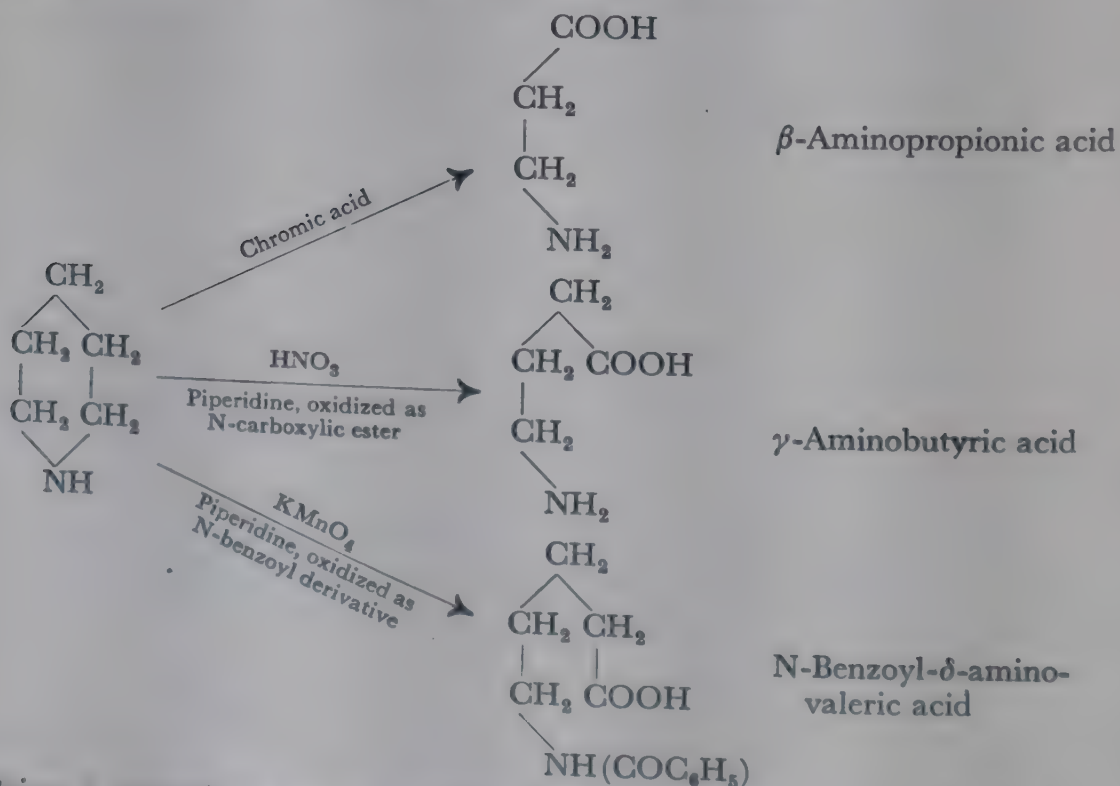


The condensation of the α - and γ -methylpyridines with aldehydes has been very useful in the preparation of pyridine derivatives, especially for the attachment of long side-chains to the pyridine nucleus (see, for example, the synthesis of coniine). According to Tschitschibabin this is also possible by acting on α - or γ -picoline with sodamide, followed by an alkyl halide. Apparently, a sodium compound of picoline, with the sodium as a substituent in the methyl group, is formed intermediately.

Pyridine derivatives with reduced pyridine nuclei are known in large numbers. The most important and best investigated of these are the hexahydro-compounds, *piperidine* and its derivatives. Many naturally occurring substances (coniine, conhydrine, piperine, nicotine, tropine, cocaine, etc.), which will be dealt with under "alkaloids", belong to this class.

Piperidine and its simpler derivatives can usually be prepared from the corresponding pyridine bases by reduction. Sodium and alcohol, or catalytically activated hydrogen may be used as reducing agents. Several processes are also known for the cyclization of aliphatic amines directly into piperidine derivatives (see for example the conversion of pentamethylenediamine into piperidine, p. 250).

Piperidine is a strong base, similar in odour to the aliphatic amines of similar M.W., soluble in all proportions in water. It boils at 106° (757 mm) and melts at -13° . It is fairly stable towards oxidizing agents in the cold, but is slowly attacked by them when heated. According to the conditions of the oxidation, different amino-acids are formed as degradation products:



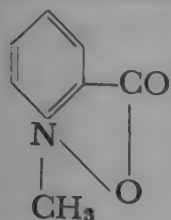
Being a secondary amine, piperidine forms a nitrosamine, N-alkyl and N-acyl derivatives. It has been very useful in bringing about condensation reactions and is often used for this purpose.

The hexahydrogenated methylpyridines are called *pipecolines* (α , β , γ).

Carboxylic acids of the pyridine series with one, two, and even three carboxyl groups are often met with amongst the oxidation products of alkaloids and quinoline compounds. They have played an important part in the elucidation of the constitution of these substances. Their names and origin are given in the table below:

	m.p.	Prepared from:
Picolinic acid = α -pyridinecarboxylic acid	135°	α -Picoline
Nicotinic acid = β -pyridinecarboxylic acid	232°	Nicotine
<i>iso</i> Nicotinic acid = γ -pyridinecarboxylic acid	317°	Cinchomeric acid
Quinolinic acid = α,β -pyridinedicarboxylic acid	175–190°	Quinoline
Cinchomeric acid = β,γ -pyridinedicarboxylic acid	257–258°	Quinine, Cinchonine
Lutidinic acid = α,γ -pyridinedicarboxylic acid	248–250°	α,γ -Lutidine
Berberonic acid = α,β',γ -pyridinetricarboxylic acid	243°	Berberine
α -Carboxycinchomeric acid = α,β,γ -pyridine-tricarboxylic acid	250°	Quinine, Cinchonine.

Pyridine- β -carboxylic acid diethyl-amide is used in medicine under the names *nikethamide* or *coramine* as an important, water-soluble substitute for camphor.



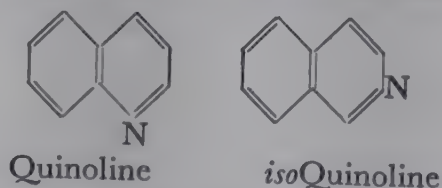
Homarine

The base *homarine* is found in the muscles of lobsters (*Homar homerus*) and in the extract from mussels (*Arca noæ*). It is picolinic acid methylbetaine. By heating it for several hours with concentrated hydrochloric acid at 200°, it gives picolinic acid.

Hydrogenated pyridine carboxylic acids are also closely related to plant bases. The alkaloid *arecaidine* (see ch. 66,3) is a N-methyltetrahydronicotinic acid; an optically active piperidine- β,γ -dicarboxylic acid is encountered in *loiponic acid*, a degradation product of the cinchona alkaloids, and piperidine- α,α' -dicarboxylic acid is found as a fission product of the alkaloid scopolamine (see ch. 67,1) and is therefore give the name *scopolinic acid*.

Quinoline compounds

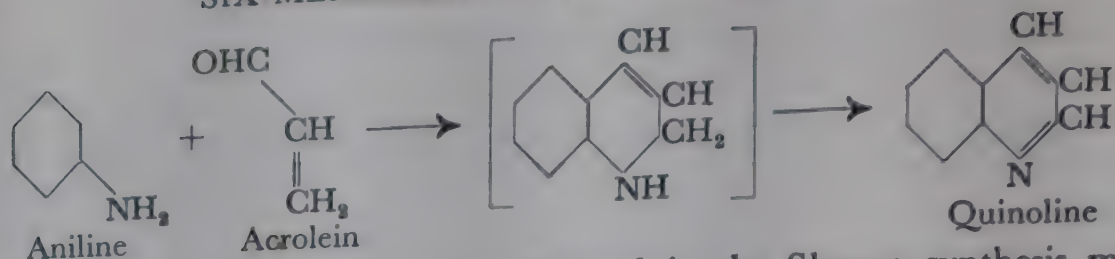
The pyridine nucleus can be imagined to condense with the benzene ring in the *ortho*-position in two ways, giving rise to *quinoline* and *isoquinoline*, respectively:



Numerous derivatives of both parent substances are known. We have already encountered some of them in connection with the organic dyes, and many others will be considered in the chapter on alkaloids.

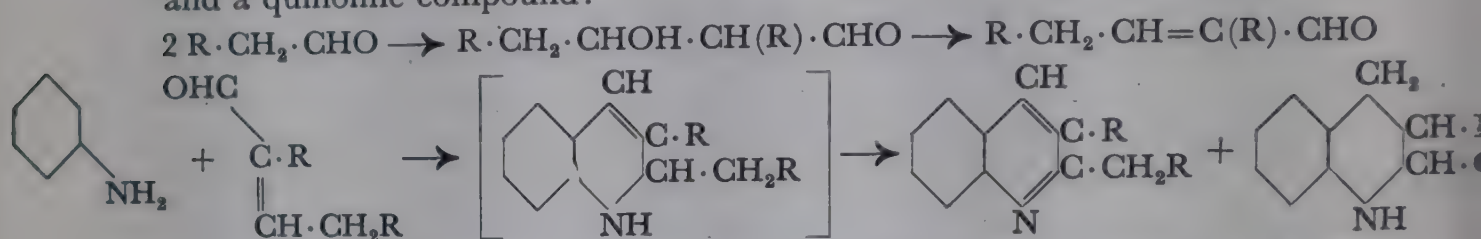
Of the *syntheses of quinoline*, which are of general application, three merit our attention:

1. **SKRAUP'S SYNTHESIS.** An aromatic amine having a free *ortho*-position is heated with glycerol, sulphuric acid, and an aromatic nitro-compound (usually that corresponding to the amine used). The sulphuric acid removes water from the glycerol, forming acrolein (see p. 169) which combines with the amine to form a dihydroquinoline derivative. This is finally dehydrogenated to quinoline by the added nitro-compound:



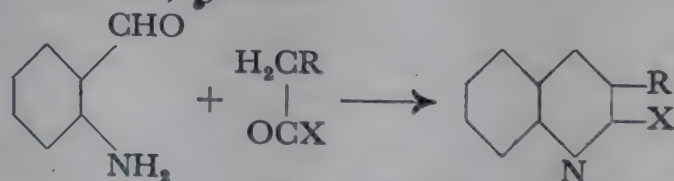
The yields of quinoline compounds obtained in the Skraup synthesis may be improved by the addition of oxidation catalysts (e.g. vanadic acid) or dehydration catalysts (Al_2O_3 , ThO_2).

2. DÖBNER AND VON MILLER'S SYNTHESIS. An aromatic amine is heated with concentrated hydrochloric acid and 2 mols. of an aldehyde. The two aldehyde molecules probably combine first as in an aldol condensation to a β -hydroxyaldehyde, which is converted into an α,β -unsaturated aldehyde by elimination of water. This enters into reaction with the aromatic amine, just as the acrolein does in the Skraup synthesis. The condensation product is a dihydroquinoline derivative, which finally disproportionates into a tetrahydroquinoline derivative and a quinoline compound:



According to this interpretation in the course of the reaction, the Skraup synthesis appears as a special case of the Döbner-von Miller synthesis. It is obvious that the latter can only be used for the synthesis of *homologues* of quinoline and not for quinoline itself.

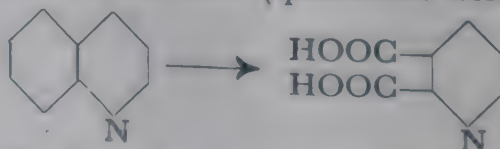
3. P. FRIEDLÄNDER'S SYNTHESIS. This consists in the condensation of *ortho*-aminobenzaldehyde with aldehydes or ketones, which contain a CH_2 -group adjacent to the CO-group: $-\text{CH}_2 \cdot \text{CO}-$. The reaction takes place in alkaline solution, and is likewise fairly general:



(R and X = H or organic radical)

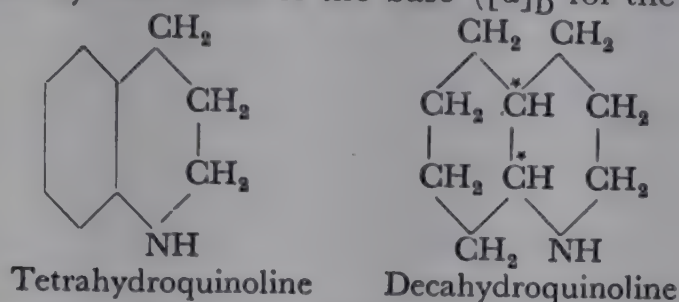
QUINOLINE and its homologues are found in coal-tar, and are prepared from it in addition to being made synthetically. It is a weak tertiary base with a sharp, characteristic smell, almost insoluble in water. It boils at 238° , and melts at -22.6° . Recently, quinoline, 2-methylquinoline, 2-*n*-amylquinoline, and some other related quinoline bases (4-hydroxy-2-*n*-amylquinoline, 4-methoxy-2-*n*-amylquinoline, etc.) have been detected in angostura bark.

The above-mentioned syntheses leave no doubt as to the constitution of quinoline. Oxidation with potassium permanganate destroys the benzene nucleus, forming pyridine- α,β -dicarboxylic acid (quinolinic acid):

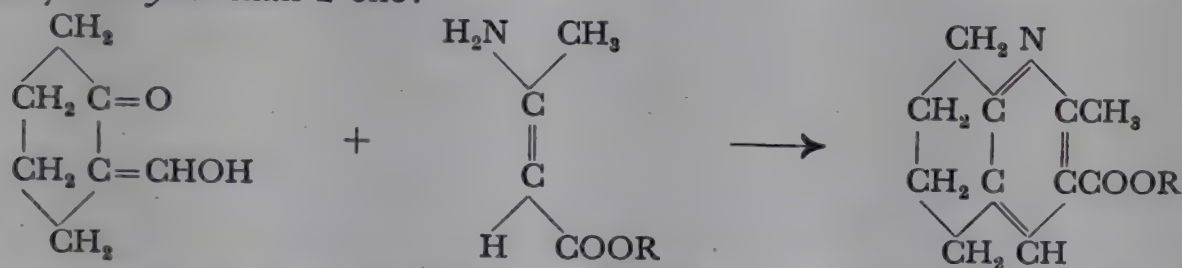


The reduction of the base has been the subject of many investigations.

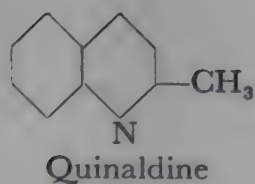
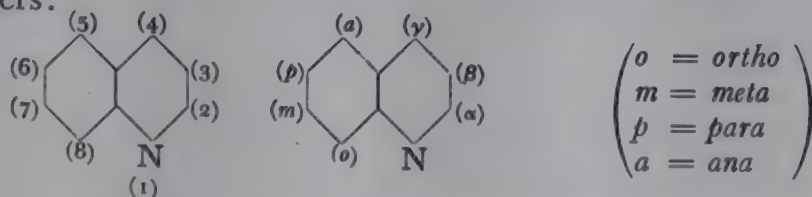
Hydrogenation of the pyridine half takes place first, no matter whether sodium and alcohol, tin and hydrochloric acid, or hydrogen with a catalyst is used for the reduction. The product is *tetrahydroquinoline*, a strong secondary base, b.p. 248° , which shows many analogies with piperidine. By further hydrogenation, e.g. with hydrogen in the presence of nickel or palladium, the benzene half of the molecule becomes fully reduced. The *decahydroquinoline* thus formed has all the characteristics of an aliphatic secondary amine, including the smell and strong basic power. It crystallizes well. It melts at 48° , and boils at 204° (corr.) at 714 mm. Its two asymmetric carbon atoms mean the existence of optical isomerides; these are indeed obtained by resolution of the base ($[\alpha]_D$ for the *trans*-form = $\pm 4.5^{\circ}$ in alcohol):



On dehydrogenation of the decahydroquinolines with platinum at high temperatures (up to 300°), *bz*-tetrahydroquinoline is formed (i.e. the quinoline derivative tetra-hydrogenated in the benzene nucleus). Such compounds can be obtained more simply by the condensation of β -aminocrotonic ester with hydroxymethylene-*cyclohexan*-2-one:

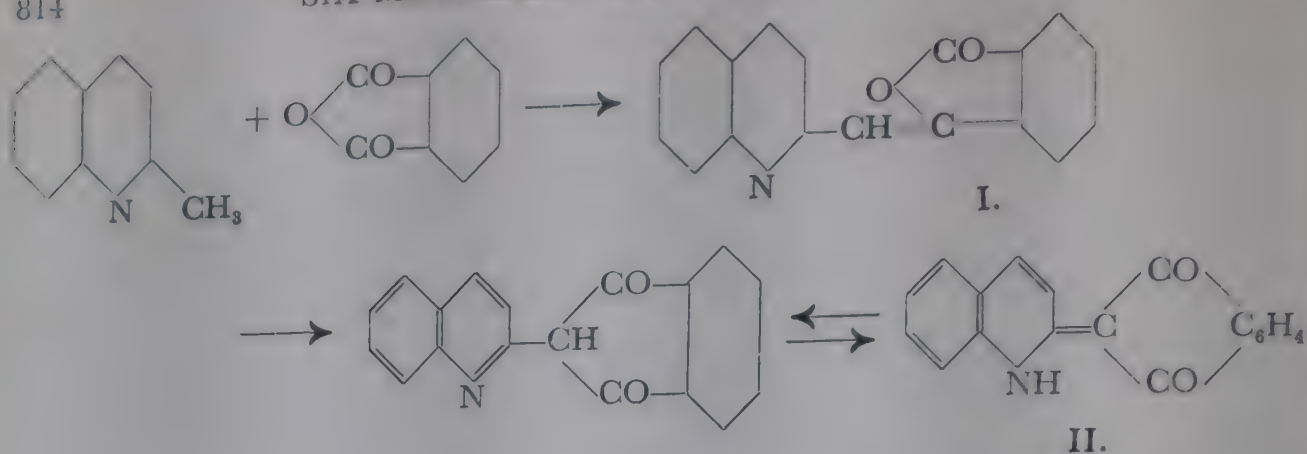


HOMOLOGUES OF QUINOLINE can be prepared by the synthetic methods described above, which give rise both to derivatives in which the side chains are in the pyridine half, and to those which have a substituted benzene nucleus. The various positions in the quinoline molecule are indicated either by numbers, or by Greek or Roman letters:



α -Methylquinoline or *quinaldine* (b.p. $246\text{--}248^{\circ}$ at 755 mm) is very easily prepared by the Döbner-von Miller reaction, using aniline and acetaldehyde. It is one of the best-investigated quinoline compounds. The hydrogen atoms of the methyl group in the α -position are reactive, like those of the corresponding pyridine derivative. Quinaldine can thus condense with aldehydes and similar compounds.

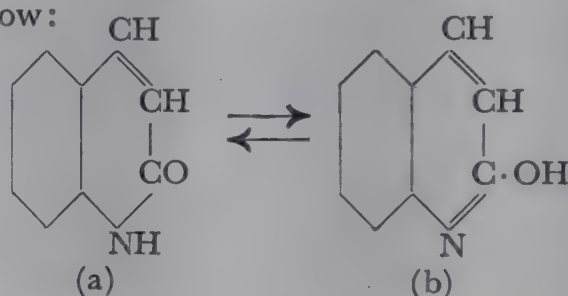
A compound of this kind, which finds practical application as a dye, is *Quinoline yellow*. Quinaldine, phthalic anhydride, and zinc chloride give a mixture of I and II, II being formed at the expense of I if the heating is stronger. The sodium salt of its disulphonic acid is the yellow dye "Soluble quinoline yellow". It is fast to light.



γ -Methylquinoline, *lepidine* (b.p. 258–260° at 742 mm), was first obtained as a decomposition product of cinchona alkaloids. Its methyl group also has mobile hydrogen atoms, which can, for example, be replaced by sodium by treating the compound with sodamide. (Those of quinaldine react in the same way.)

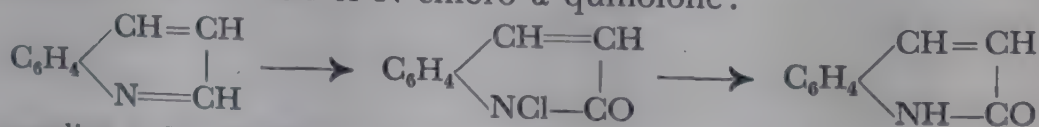
Methyl derivatives of quinoline (e.g. 2:3-dimethyl-, 2:4-dimethyl-, 2:8-dimethyl-, and 2:4:8-trimethylquinoline) have been isolated from Californian mineral oil.

Of the group of *hydroxyquinolines*, α -hydroxyquinoline or *carbostyryl* (m.p. 200°) may be mentioned. It is a compound which has played a not unimportant part in the investigation of the problem of tautomerism. It reacts in the two tautomeric forms shown below:



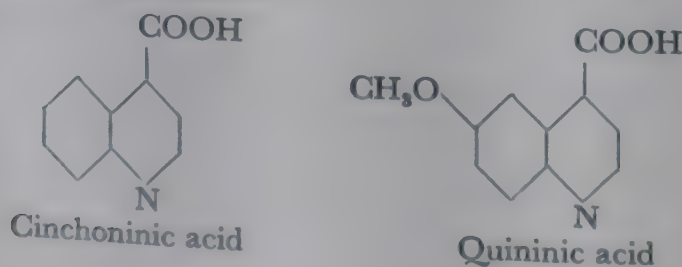
Alkyl derivatives derived from both these forms are known. A mixture of N-ethylcarbostyryl with carbostyryl O-ethyl ether is formed by the action of ethyl iodide and alkali on α -hydroxyquinoline. The O-ether alone is obtained by the action of ethyl iodide on the silver compound of carbostyryl.

A satisfactory method of preparing carbostyryl itself involves the oxidation of quinoline with bleaching powder. The reaction appears to take place with the intermediate formation of N-chloro- α -quinolone:



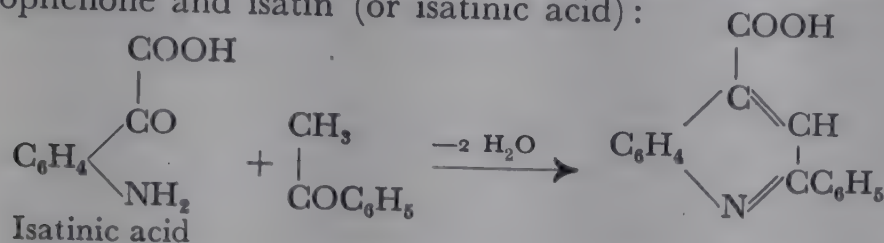
According to Tschitschibabin, carbostyryl is obtained in 80% yield if barium oxide is allowed to act upon quinoline at 225°.

Of the QUINOLINE CARBOXYLIC ACIDS, *cinchoninic acid*, quinoline- γ -carboxylic acid, and its *p*-methoxy-derivative, *quininic acid*, are of special interest on account of their close relationship with the alkaloids cinchonine and quinine. They are formed by oxidation of the latter:



On distillation with lime they give quinoline and *p*-methoxyquinoline, respectively. The position of the carboxyl group in cinchoninic acid may be inferred from its oxidative degradation to α,β,γ -pyridinetricarboxylic acid.

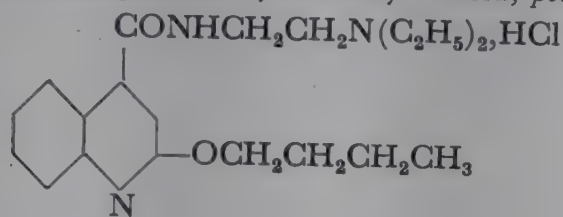
2-Phenylcinchoninic acid (2-phenylquinoline-4-carboxylic acid) causes increased excretion of urine, and is therefore much used in the treatment of gout. It is known in commerce as *atophan*. It is synthesized by heating equimolecular quantities of aniline, benzaldehyde, and pyruvic acid, or by the alkaline condensation of acetophenone and isatin (or isatinic acid):



The methyl ester of atophan occurs in commerce under the name *novatophan*, and the allyl ester as *atoquinol*.

γ -Hydroxyquinoline- α -carboxylic acid, or *kynurenic acid*, is of biological interest on account of its occurrence in the urine of dogs and its relationship with tryptophan (see p. 787).

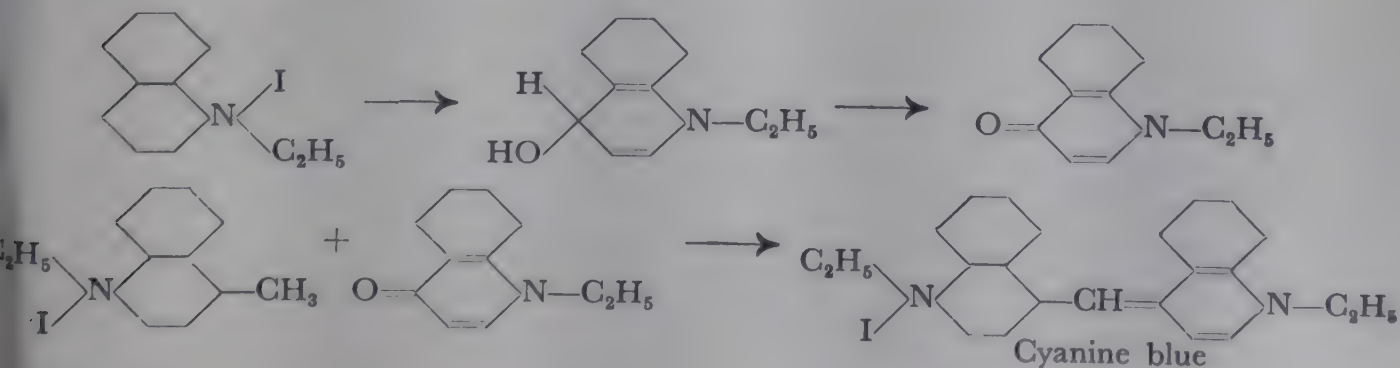
A derivative of α -hydroxyquinoline- γ -carboxylic acid, *percaine*,



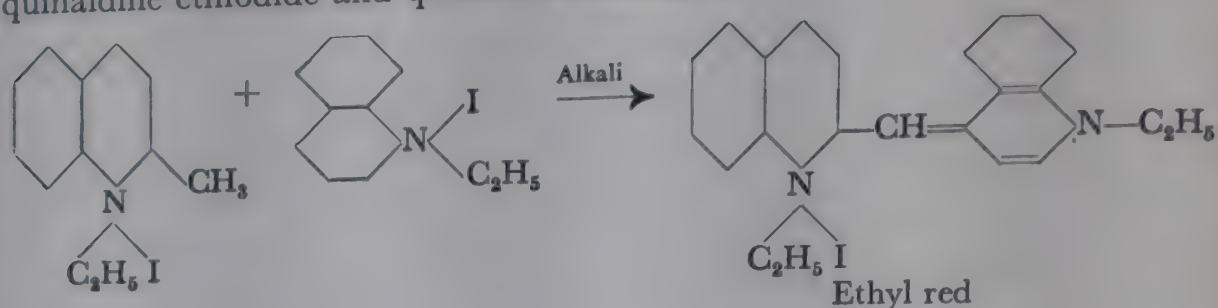
is of interest as a powerful anæsthetic.

The compounds of quinoline, quinaldine, and lepidine with alkyl halides have become the starting points for the preparation of an important class of dyes, comprising the so-called *cyanine and isocyanine dyes*. These compounds were first reported by C. G. Williams as long ago as 1860. Outstanding contributors to their subsequent investigation have been, among others, A. W. Hofmann, Nadler, Hoogewerff and van Dorp, Spaltenholz, Miethe, W. König, O. Fischer, and A. Kaufmann. On account of their great sensitivity towards acids and lack of fastness to light they are not used for actual dyeing, but they are excellent sensitizers for the preparation of panchromatic photographic plates.

The *cyanines* are blue; a γ -methyl group of an alkyl-quinolinium halide takes part in the condensation by which they are prepared. For example, lepidine ethiodide and quinoline ethiodide give rise to *Cyanine blue*. The quinoline compound is first converted by alkali into the pseudo-base, which, by interaction with oxygen, gives the corresponding quinolone, which finally condenses with the lepidine ethiodide:



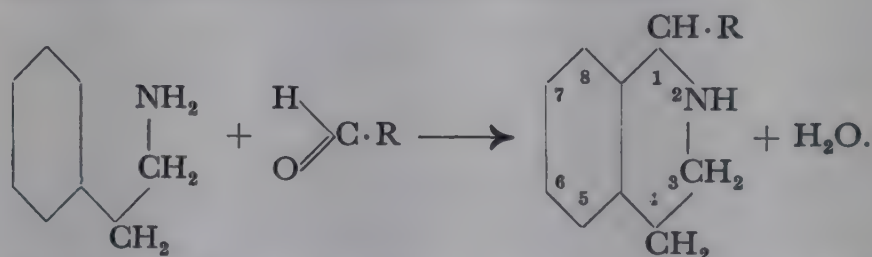
In the formation of the red *isocyanines* it is α -methyl groups of quinoline moieties which are involved. The widely-known *Ethyl red* is the reaction product of quinaldine ethiodide and quinoline ethiodide:



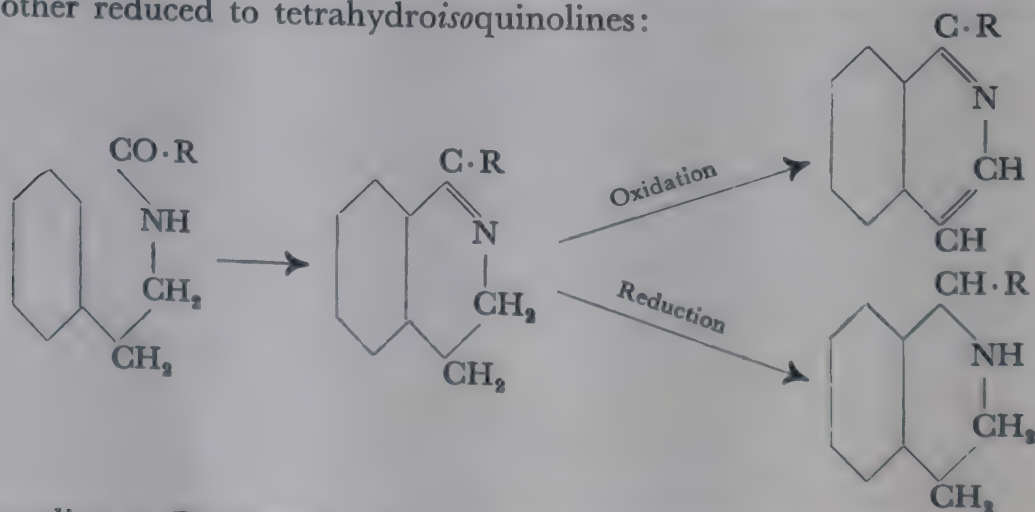
Isoquinoline

The *isoquinoline* ring, particularly in the hydrogenated form, but also to some extent in the non-hydrogenated form, is the basis of numerous alkaloids. (See the *isoquinoline* alkaloids, ch. 69). The base was discovered in coal-tar (Hoogewerff and van Dorp) where it occurs in small quantities.

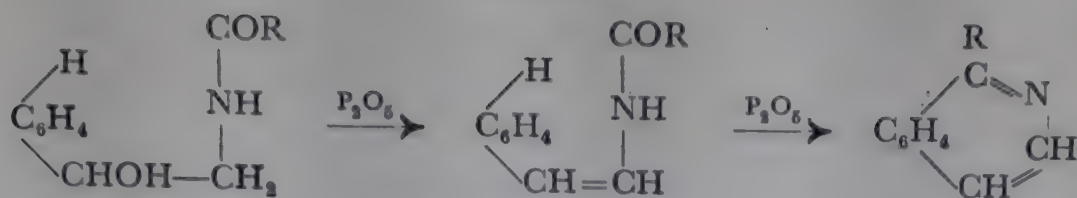
Of the synthetic methods for preparing *isoquinoline* compounds, two in particular are of general use (Bischler and Napieralsky, A. Pictet, Decker). They are very similar to each other. One depends on the condensation of β -phenyl-ethylamine and its derivatives with aldehydes (condensing agent, hydrochloric acid), and leads to tetrahydro*isoquinoline* compounds:



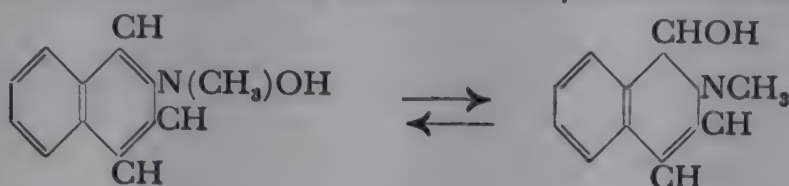
The other consists in the elimination of water from acylated β -phenyl-ethylamine derivatives, which is effected, for example, by boiling in benzene solution with phosphorus pentoxide. In this reaction dihydro*isoquinoline* derivatives are formed, which on the one hand can be oxidized to *isoquinoline* compounds, and on the other reduced to tetrahydro*isoquinolines*:



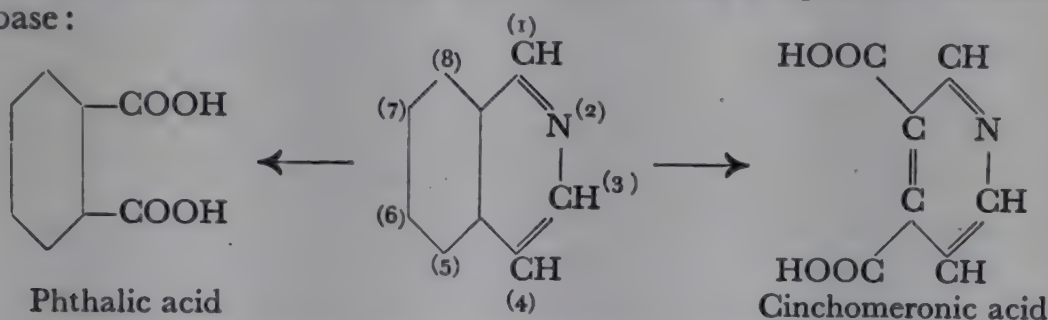
According to Pictet and Gams, non-hydrogenated *isoquinoline* derivatives may also be formed by the action of phosphorus pentoxide on acyl derivatives of phenyl-aminomethyl-carbinol, which are produced by reduction of those of ω -aminoacetophenone:



*iso*QUINOLINE is a fairly strong base; m.p. 24° ; b.p. 240° . Its smell is somewhat similar to that of benzaldehyde. It reacts violently with alkyl halides giving quaternary salts. The parent quaternary *iso*quinolinium bases can, like the analogous quinolinium compounds, undergo isomerization to carbinol forms, which are in equilibrium with the ammonium hydroxide forms:



The oxidation of *iso*quinoline with potassium permanganate gives phthalic acid and cinchomeric acid. This rupture of the ring is a proof of the constitution of the base:

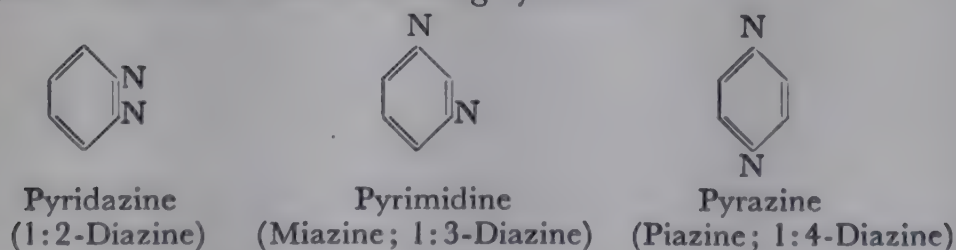


By reduction of *iso*quinoline (sodium and alcohol), tetrahydro*iso*quinoline is formed. It has the character of an aliphatic, secondary amine, b.p. 230° . Its constitution is made clear by its synthesis from β -phenyl-ethylamine and formaldehyde (see the first of the general syntheses).

CHAPTER 62. SIX-MEMBERED HETEROCYCLIC RINGS WITH TWO OR MORE HETERO-ATOMS

Diazines

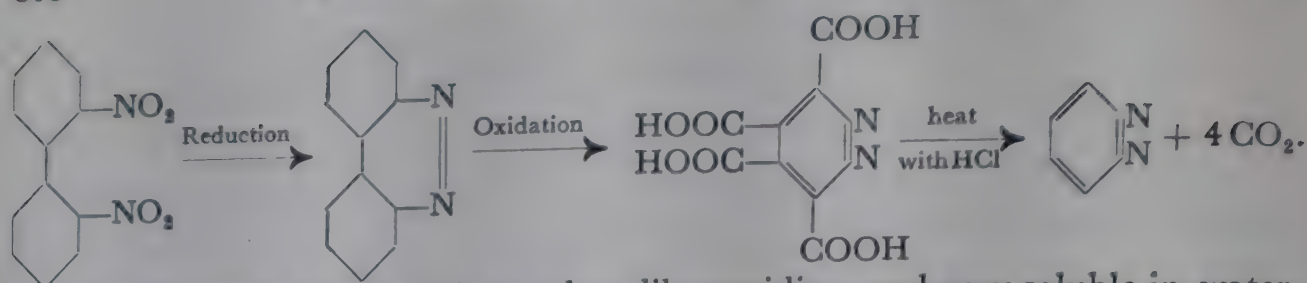
Six-membered heterocyclic rings with two nitrogen atoms in the ring are known as *diazines*. There are three such ring systems:



The *pyridazines* command the least interest. The parent substance, pyridazine itself, may be obtained by various methods, e.g. from maleic dialdehyde and hydrazine:

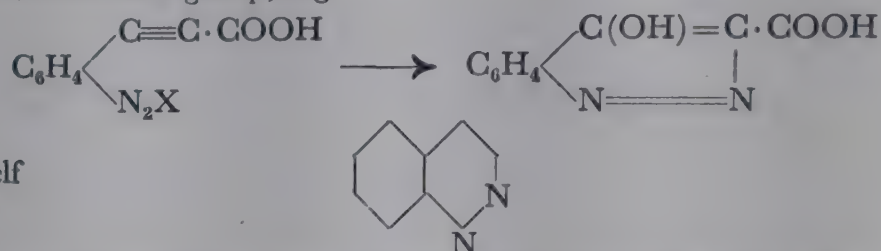


or from *o,o'*-dinitrophenyl in the following way:



Pyridazine is a base, with an odour like pyridine, and very soluble in water. M.p. -6.4° ; b.p. 207.4° at 762 mm (strongly associated). By reduction with sodium and alcohol it is broken down to tetramethylenediamine.

Cinnoline is composed of a benzene and a pyridazine ring both condensed in the *ortho*-position. Its derivatives can be obtained from aromatic diazo-compounds which have an unsaturated side chain, with its double or triple bond adjacent to the benzene ring, in the *ortho*-position to the diazo-group, e.g.:



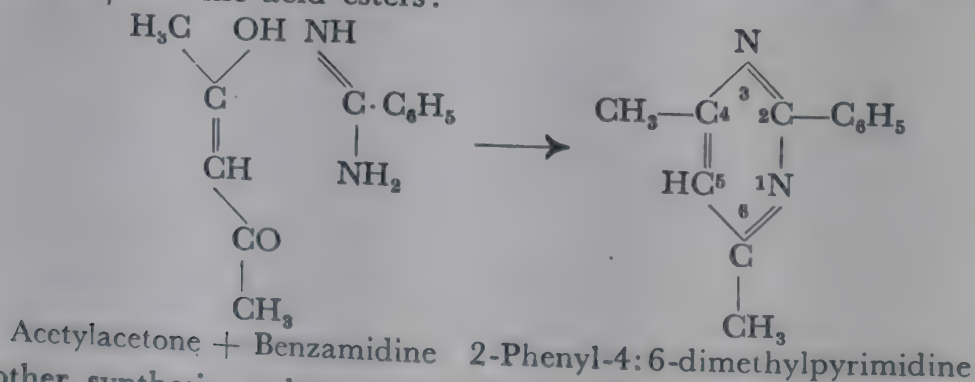
Cinnoline itself

is a bright yellow compound, which forms stable monobasic salts and combines with methyl iodide to give a mono-methiodide. M.p. $38-39^\circ$.

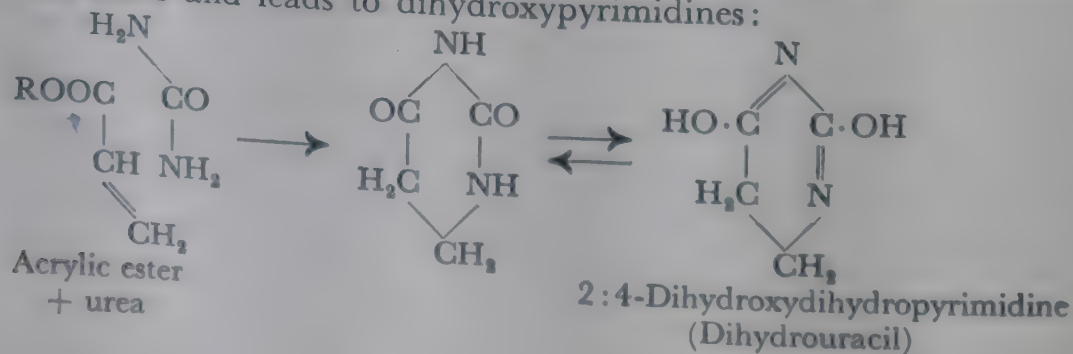
Pyrimidines. Amongst the diazines, the pyrimidine or miazine group stands out through the physiological importance of its compounds. Important plant bases, particularly the purine and uric acid derivatives (see p. 823), as well as certain fission products of the nucleic acids (uracil, thymine, cytosine) are derived from the pyrimidine nucleus.

In the pyrimidines the two nitrogen atoms have the same mutual positions as they have in urea and the amidines. The latter compounds may therefore be used for the synthesis of the pyrimidine bases.

A method of formation depends on the condensation of amidines with β -diketones or β -ketonic acid esters:

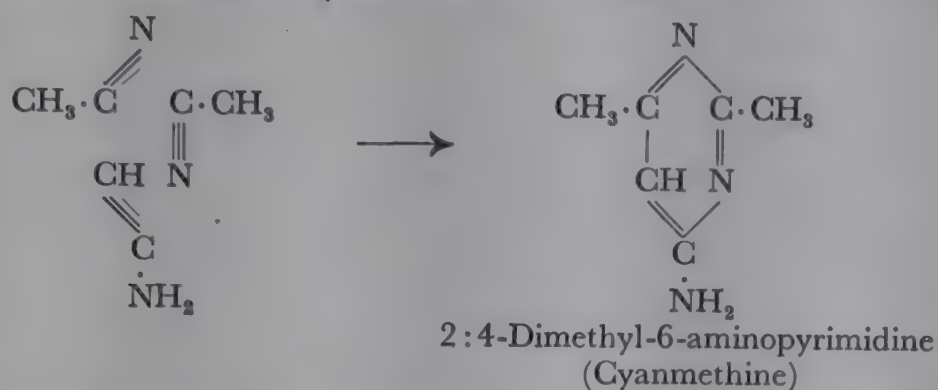


Another synthesis makes use of the addition of urea to α,β -unsaturated carboxylic acid esters and leads to dihydroxypyrimidines:



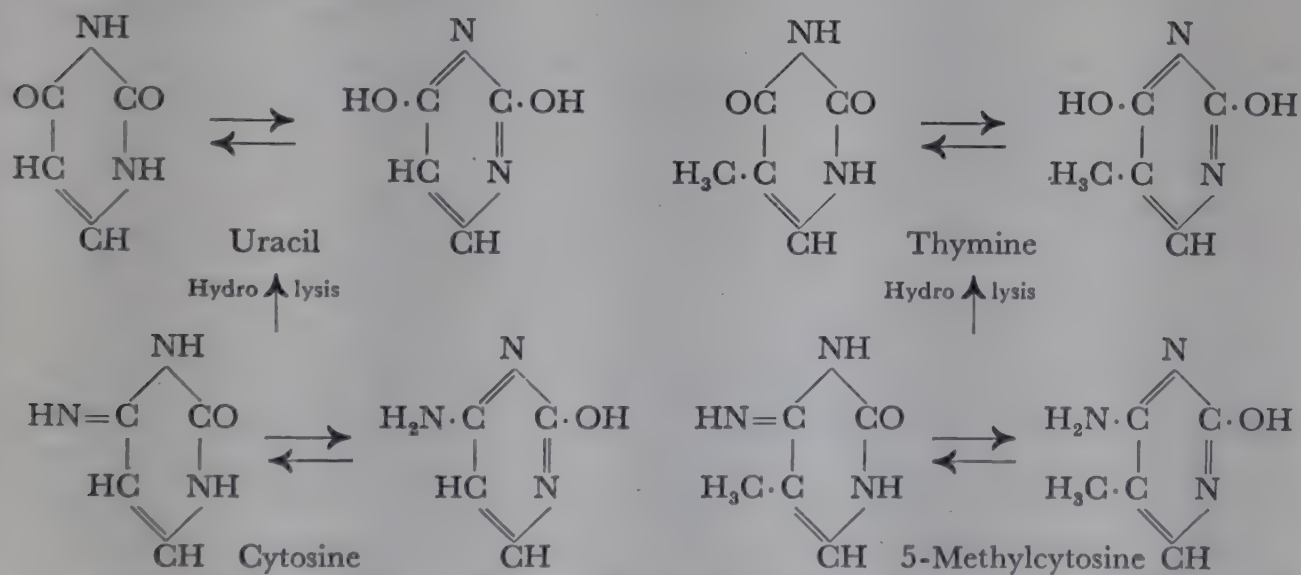
PYRIMIDINE is a quite stable, well-crystallized compound (m.p. 20–22°; b.p. 124° (corr.)), which dissolves in water giving a *neutral* solution, but forms salts with acids. Its homologues possess similar properties.

Certain *amino-derivatives* of pyrimidine homologues are obtained in a peculiar way. They are formed by the polymerization of aliphatic nitriles (brought about by sodium). To explain their formation in this reaction it may be assumed that of the three molecules of alkyl cyanide which combine, one reacts as an amino-acetylene derivative, $\text{CH}_3\text{C}\equiv\text{N} \rightleftharpoons \text{CH}\equiv\text{CNH}_2$:



These compounds are called *cyanalkines* (cyanmethine, -ethine, etc.). They are strong bases, and crystallize well.

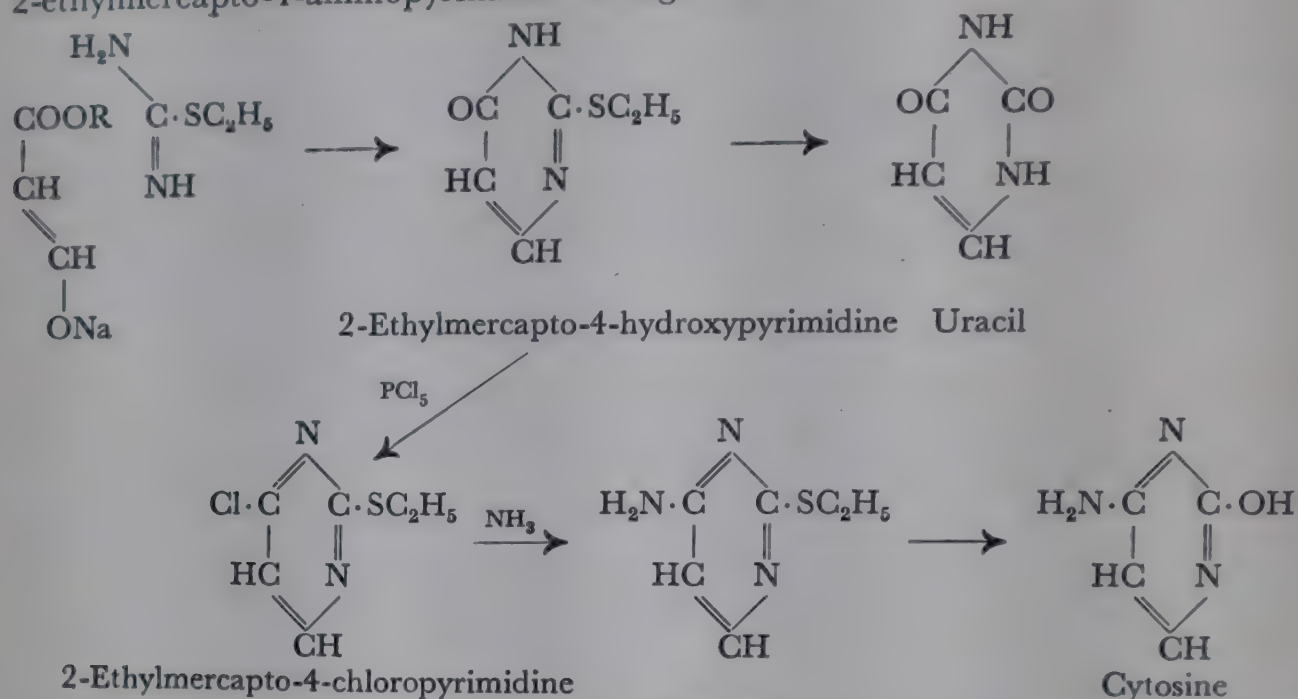
DIHYDROXYPYRIMIDINES and AMINOHYDROXYPYRIMIDINES. Two dihydroxy- and two aminohydroxypyrimidines have been found amongst the hydrolytic fission products of various nucleic acids (see p. 829). They are *uracil* = 2:4-dihydroxypyrimidine, *thymine* = 2:4-dihydroxy-5-methylpyrimidine, *cytosine* = 2-hydroxy-4-aminopyrimidine, and *5-methylcytosine* = 2-hydroxy-4-amino-5-methylpyrimidine. According to T. B. Johnson, it may be that only cytosine and methylcytosine are primary products, taking part as such in the building up of the nucleic acids, whilst uracil and thymine are formed from them by hydrolytic fission, brought about either by acids or by enzymes. In all four cases, tautomeric forms may be envisaged:



The constitution of these biologically important compounds has been substantiated by synthesis. Thus, uracil is obtained, for example, by the oxidation of 2:4-dihydroxy-dihydropyrimidine (dihydrouracil), the product of the interaction of urea and acrylic acid, whose formation has been described above (E. Fischer). The oxidation is carried out with bromine. A monobromohydrouracil is formed

as intermediate, from which pyridine removes a molecule of hydrogen bromide.

A second synthesis (Wheeler and Merriam) starts with S-ethyl-pseudo-thiourea, which is condensed with the sodium salt of formylacetic ester. The first reaction product is ethylmercapto-hydroxypyrimidine. It breaks down on heating with hydrochloric acid to give uracil, but may also be converted by the series of reactions outlined below into cytosine, 2-ethylmercapto-4-chloropyrimidine and 2-ethylmercapto-4-aminopyrimidine being formed as intermediates:



The very simple synthesis of uracil due to Baudisch depends on the condensation of urea with malic acid and sulphuric acid. Formylacetic acid, formed from malic acid, is an intermediate product:



Thymine is especially easily prepared by the reduction of methylcyanoacetylurea with hydrogen and platinum:



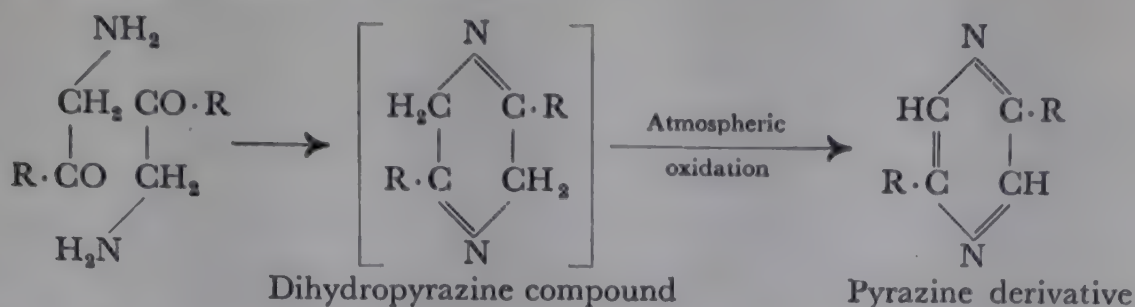
Uracil and thymine, the first discovered by A. Ascoli, and the second by Kossel, are neutral. Their melting points are 338° and 340° respectively. Cytosine (Kossel) decomposes above 320°. On treatment with nitrous acid it is converted into uracil by deamination.

The important ureides of several dicarboxylic acids, *barbituric acid*, *alloxan*, etc., must also be classed as hydroxy derivatives of pyrimidine. They have already been described in earlier parts of this book.

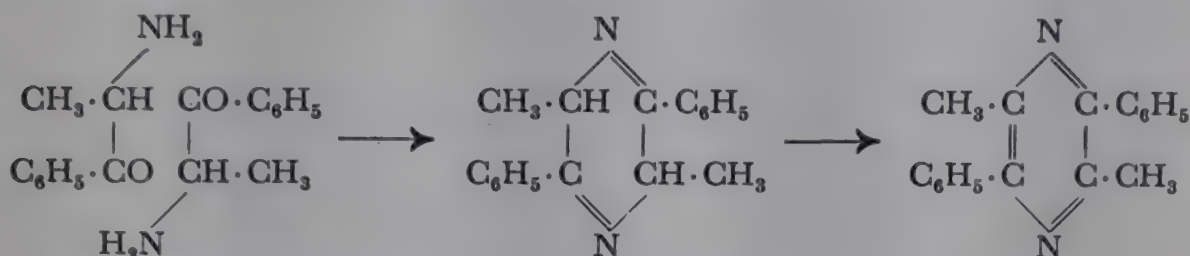
Of the condensed pyrimidine systems the purines are the most important; see the purine group, p. 823 ff.

Pyrazines. The heterocyclic ring system of the pyrazines has been encountered before. A series of dyes in which it occurs condensed with benzene nuclei, have already been dealt with in connection with other groups of dyes; see, for example, the phenazine dyes, indanthrene, etc. We will limit ourselves here to the methods of formation and properties of some simple pyrazine derivatives.

These are generally readily formed from α -amino-ketones, $R \cdot CO \cdot CH_2NH_2$, which are not stable in the free state, but rapidly condense, *via* the very readily oxidized dihydropyrazines to pyrazines:



Those dihydropyrazine derivatives which are produced by ring closure from α -amino-ketones of the formula $R \cdot CO \cdot CHR' \cdot NH_2$, are somewhat less sensitive to oxidation and can therefore be isolated:



Dialkylated α -amino-ketones, $R \cdot CO \cdot C(\text{Alkyl})_2 \cdot NH_2$, are stable, i.e. they are less readily converted into pyrazine compounds (Gabriel).

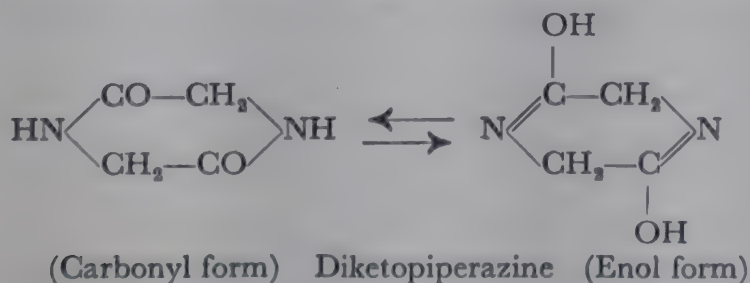
The simple pyrazines are readily volatile compounds, which can be distilled and have an aromatic smell. That of pyrazine somewhat recalls heliotrope. These compounds dissolve readily in water with formation of hydroxides. In spite of the two nitrogen atoms present, they will only add on one molecule of alkyl halide. The melting point of pyrazine is $53-55^\circ$, and its boiling point, 116° .

All the pyrazines are readily reduced to the hexahydrides, *piperazine* and its derivatives.

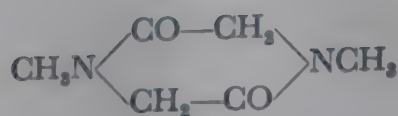
Piperazine is a strong base, readily soluble in water, which gives well-crystallized salts; m.p. 104° , b.p. 145° . In its general chemical behaviour it corresponds to the aliphatic secondary amines.

In recent times certain oxy-derivatives of piperazine, *2:5-dioxopiperazines*, or *2:5-diketopiperazines*, have been thoroughly investigated. The reason for this rests in the observation that 2:5-diketopiperazines are found among the products of the acid and enzymic hydrolysis of proteins (E. Fischer, Abderhalden). It is, however, not yet certain how far these substances occur as such in the intact proteins, since they are formed with extraordinary ease from amino-acids and dipeptides, and their occurrence amongst the decomposition products of proteins may therefore be due to secondary processes.

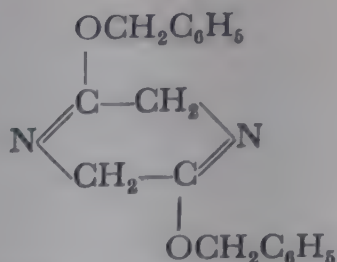
2:5-Diketopiperazine and its derivatives exhibit tautomerism:



Derivatives of both forms are known, e.g.



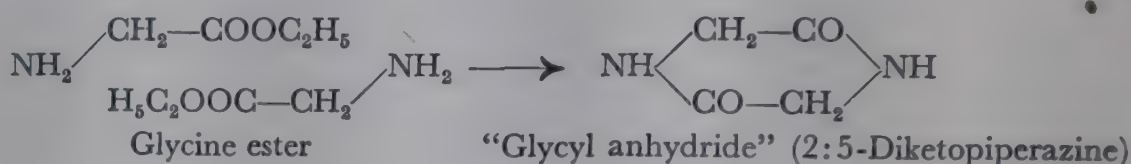
N,N'-Dimethyl-2:5-diketopiperazine



O,O'-Dibenzyl 2:5-dihydroxy-dihydropyrazine

Even if diketopiperazines are involved to an appreciable extent in protein structures, the question still remains as to whether they are present in the carbonyl or the enol form.

2:5-Diketopiperazines are usually prepared from the free esters of the amino-acids, which spontaneously condense on long keeping and more rapidly on warming, giving diketopiperazines with elimination of alcohol (Curtius and Goebel):

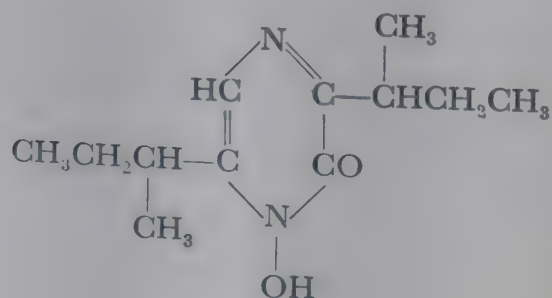


These amino-acid anhydrides are also formed on heating the free amino-acids in dilute glycerol solution to about 170° or on prolonged warming of dipeptides with dilute hydrochloric acid.

Diketopiperazines are solid, well-crystallized compounds, which react neutral and in some instances give well-characterized metal salts.

On reduction with sodium and alcohol, 2:5-diketopiperazines give piperazines, but in small yield. This process is of importance in deciding their constitution. The simple members in particular are very sensitive to alkalis; by addition of the elements of water, they are cleaved to dipeptides. Ordinary 2:5-diketopiperazines and their N,N-dialkyl derivatives are hydrolysed by acids only on long boiling. O,O'-Dibenzyl dihydroxy-dihydropyrazine (see above), derived from the tautomeric form, behaves quite differently, being decomposed in the cold even by very dilute acids to benzyl alcohol and glycine.

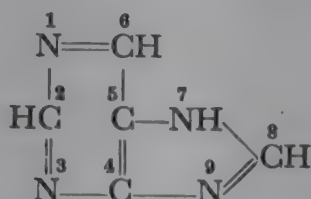
One of the naturally occurring pyrazine derivatives is *aspergillilic acid* from the micro-organism *Aspergillus flavus*; it acts as an antibiotic:



Purine compounds¹

The purine compounds form a group of very closely related compounds, whose structures are well-established, which are widely distributed in plants, and also to some extent in the animal organism. Amongst them must be included, by virtue of its structure, *uric acid* which, together with urea, is the most important nitrogenous end-product of animal metabolism. Its close connection with the other purine compounds makes it convenient to deal with it here.

Purine has the formula:



and is thus composed of an imidazole and a pyrimidine ring with two carbon atoms in common.

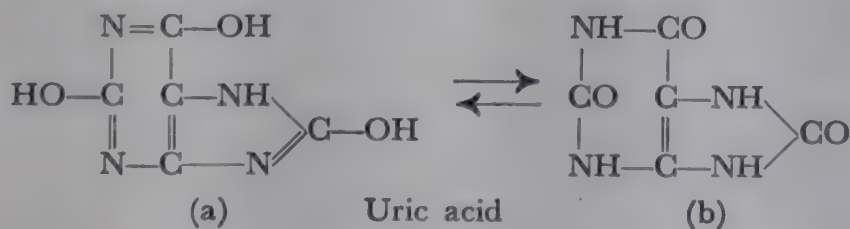
Uric acid. In the body of man and mammals uric acid only occurs in small quantities under normal conditions. There are traces of it in the blood, and small quantities are excreted in the urine. In the latter case it probably arises from the metabolism of nucleic acids (see p. 829) and is a decomposition product of various purine derivatives.

In certain pathological conditions the amount of uric acid in the body can be considerably increased, as for example, in gout, which is accompanied by the separation of uric acid in the joints. Urinary calculi and gallstones consist almost entirely of uric acid or its salts. T. Bergmann discovered the compound (1776) in urinary calculi, simultaneously with Scheele, who obtained it from the same source and from urine.

Uric acid is of special importance as a nitrogenous end product of metabolism in the organisms of reptiles and birds, where it is produced as a degradation product of proteins. It is the chief nitrogenous compound in the excrement of these animals, and is therefore also found in large quantities in guano, from which it is prepared on a large scale.

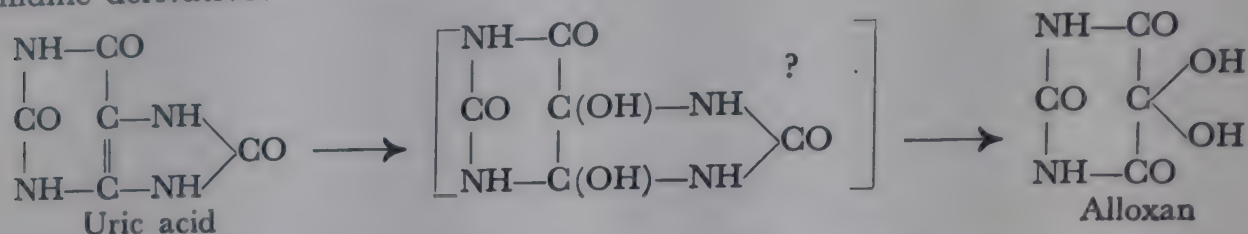
Snakes and other reptiles eliminate part of their uric acid by shedding their skins, which always contain uric acid.

The constitution of uric acid has been fully elucidated. It is 2:6:8-trihydroxy-purine, which may be written in the two tautomeric forms (a) and (b). From the absorption spectrum it is concluded that the carbonyl form (b) greatly predominates in this equilibrium:

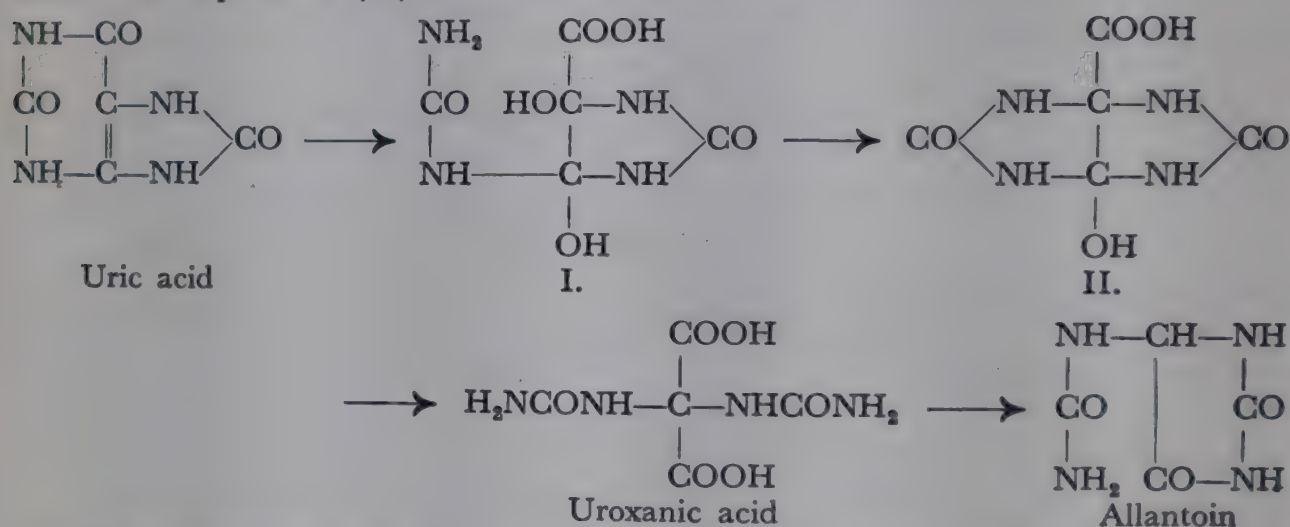


¹ See also R. FEULGEN, *Chemie und Physiologie der Nukleinstoffe nebst Einführung in die Chemie der Purinkörper*, Berlin, (1923.) — E. FISCHER, *Untersuchungen in der Puringruppe*, Berlin, (1907).

The results of the oxidative degradation of uric acid support this formula. Whilst the compound is stable — though not greatly so — to the hydrolytic action of acids and bases and to reducing agents, it is readily attacked by oxidizing agents in acid or alkaline solution. Nitric acid converts it into *alloxan* (mesoxalylurea), a glycol being possibly an intermediate decomposition product. The pyrimidine half of the uric acid is thus removed in this reaction in the form of a simple pyrimidine derivative:



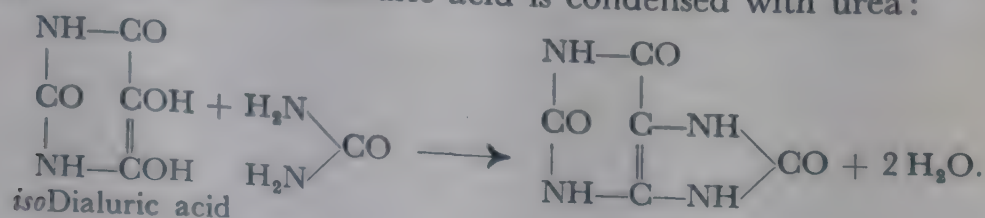
In neutral or alkaline solution the imidazole ring of the uric acid molecule is unaffected by oxidation. It appears then in the form of *allantoin*. It is probable that here again the decomposition proceeds through a glycol (I), and a further intermediate product (II), which can be isolated:



The degradation of uric acid to allantoin may be brought about by the action of an enzyme, "uricase". It is likely that, in this way, large quantities of allantoin are produced under natural conditions. The compound is often encountered in the urine of animals, especially that of carnivorous animals, but particularly in plants, where it occurs widely. It reacts neutral, is optically inactive, and melts at 238–240°. It has been possible to obtain optically active allantoin ($[\alpha]_D^{20} = -92^\circ 24'$) by fermenting the racemate with an enzyme "allantoinase" occurring in seeds (R. Fosse).

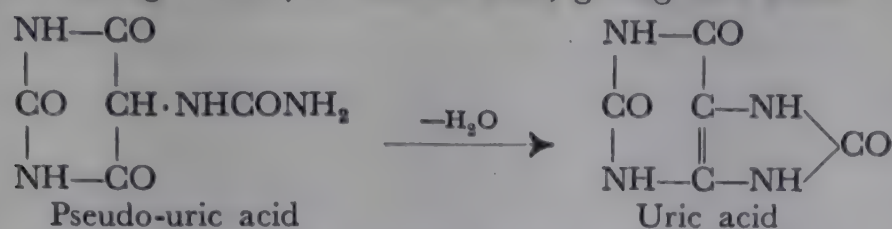
Uric acid has been synthesized by several methods:

1. The oldest synthesis, which is quite straightforward, is that of Behrend and Roosen (1888), in which *isodialuric acid* is condensed with urea:

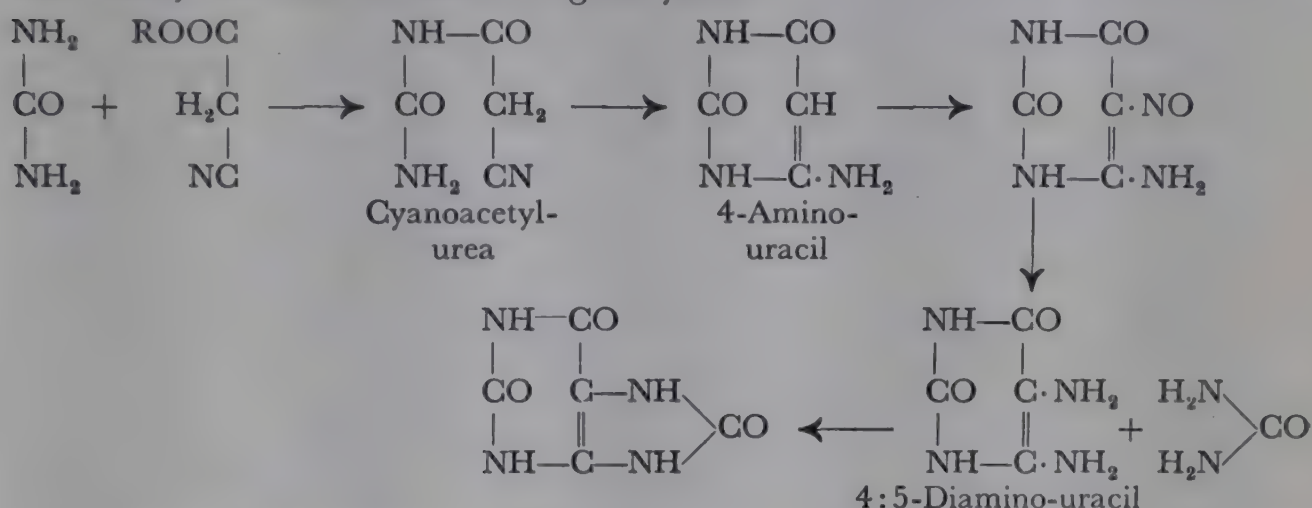


2. Of greater preparative interest is the synthesis of uric acid by E. Fischer and L. Ach. In this, "pseudo-uric acid" (see p. 279), which had been obtained by

A. von Baeyer from uramil (p. 279), was cyclized and dehydrated by fusing with oxalic acid, or boiling with hydrochloric acid, giving uric acid:



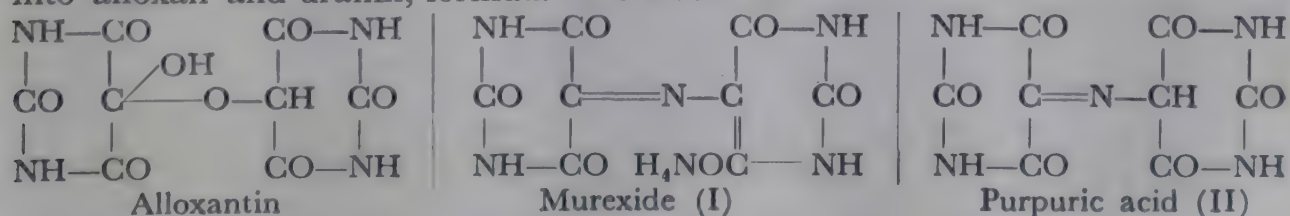
3. A very general procedure, and one which has therefore been widely and successfully used in the preparation of the purines, is that put forward by W. Traube for the synthesis of uric acid. Urea is condensed with cyanoacetic ester to cyanoacetylurea, which isomerizes under the influence of alkalis to 4-amino-2:6-dihydroxypyrimidine (4-amino-uracil). The latter is converted to 4:5-diamino-uracil through the nitroso-compound. If 4:5-diamino-uracil is fused with urea, uric acid is formed in good yield:



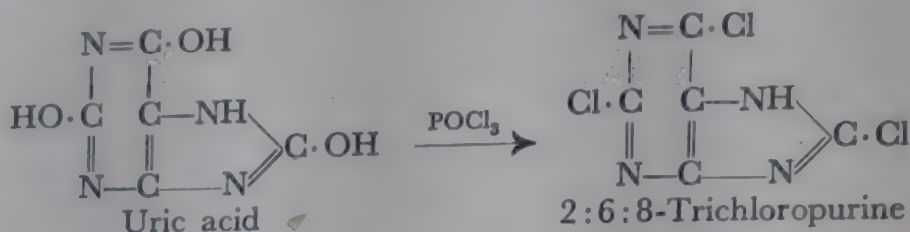
Uric acid is a white, crystalline substance, difficultly soluble in water. It has weak acidic properties. It forms two series of salts (*urates*), the primary salts with the composition $\text{M}'\text{C}_5\text{H}_3\text{O}_3\text{N}_4$, and secondary salts, $(\text{M}')_2\text{C}_5\text{H}_2\text{O}_3\text{N}_4$. The primary alkali-metal urates are very difficultly soluble in water, but possess the peculiarity of readily forming supersaturated colloidal solutions. The primary sodium salt is a constituent of urinary calculi, and primary ammonium urate occurs in the excrement of snakes, and in gallstones and urinary calculi.

The secondary alkali-metal urates are more soluble in water.

To detect uric acid the *murexide reaction* may be used. It is not, however, specific for uric acid, as many other purine bodies respond to it. Uric acid is evaporated with nitric acid, and the residue gives a purplish red colour with ammonia. This coloration is due to murexide, the ammonium salt of the so-called *purpuric acid*. By the action of nitric acid, uric acid is converted partly into *alloxantin*, a molecular compound of alloxan and dialuric acid, which may have the constitution given below (for another formulation see *Ber.*, 54, 1267); ammonia then converts this into the ammonium salt of purpuric acid (murexide), to which is allotted formula I. For free purpuric acid, which is extremely readily hydrolysed into alloxan and uramil, formula II is favoured:

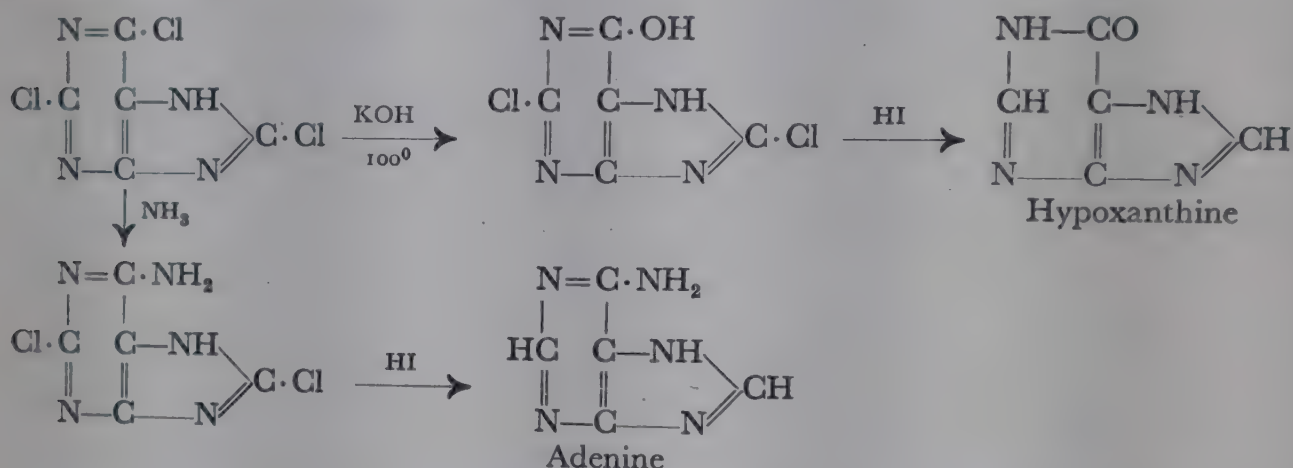


A most important stage in the preparation of many purines is the conversion of uric acid into 2:6:8-trichloropurine; this is effected with phosphorus oxychloride:

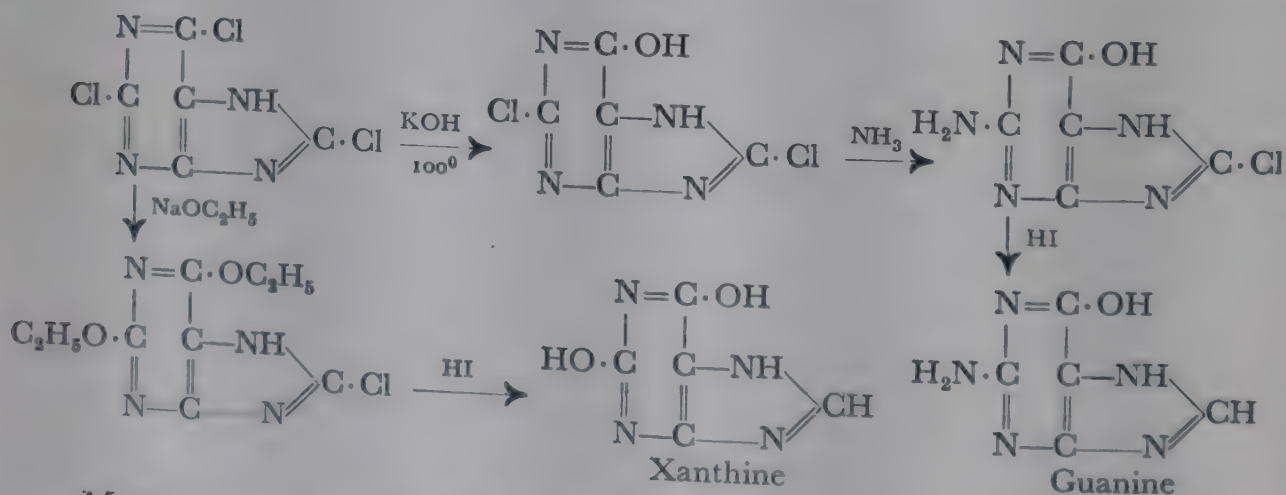


By replacing the individual chlorine atoms by OH or NH₂, E. Fischer has demonstrated a route whereby all the naturally occurring purine bases can be synthesized.

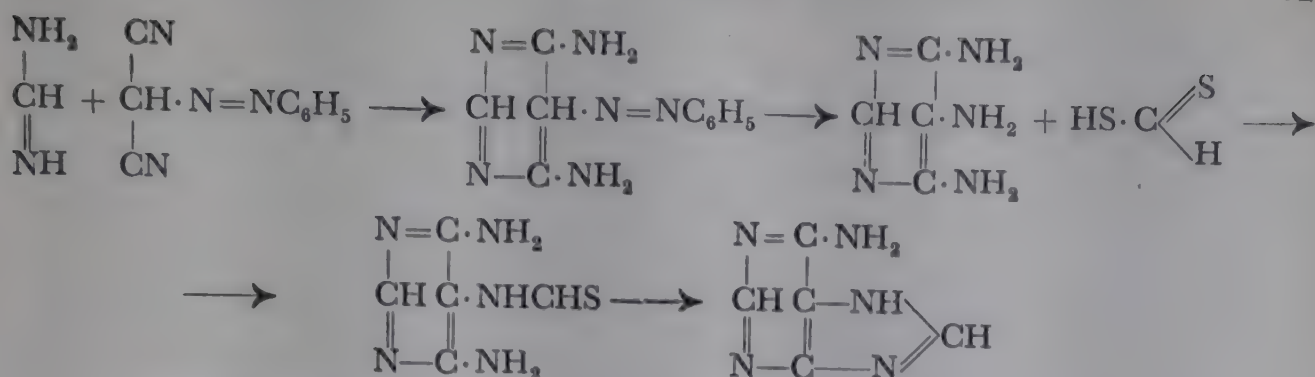
The chlorine atom in position 6 is the most reactive. By the controlled action of caustic potash it is replaced by hydroxyl, and by the action of ammonia it is replaced by NH₂. If the two remaining chlorine atoms are subsequently reduced by means of hydriodic acid, *hypoxanthine* (6-hydroxypurine) and *adenine* (6-aminopurine) are produced respectively:



The next chlorine atom in order of reactivity in 2:4:6-trichloropurine is that in the 2-position. It is therefore possible to prepare *guanine* (2-amino-6-hydroxypurine) and *xanthine* (2:6-dihydroxypurine) by the following series of reactions:



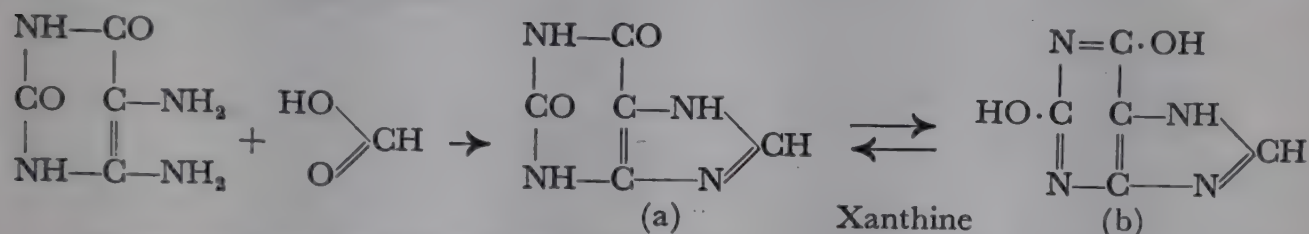
More recently, a number of other syntheses of purine derivatives have been worked out; e.g. condensation of formamidine with benzeneazo-malononitrile, followed by reduction, gives 4:5:6-triaminopyrimidine, which yields adenine when acted upon by sodium dithioformate (A. R. Todd):



1:3:7:9-Tetramethyluric acid is present in tea (T. B. Johnson) and can also be obtained synthetically.

Xanthine (2:6-dihydroxypurine). This important purine derivative is widely distributed in small quantities in plants. It accompanies caffeine in tea, and has been detected in animal excretions (urine), in the blood, and in the liver etc., and occurs also in urinary calculi, in which it was discovered by Marcet (1817).

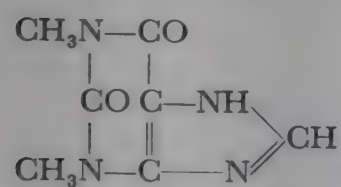
We have just dealt with its artificial formation from uric acid *via* trichloropurine. In a second synthesis, due to W. Traube, the compound is prepared from 4:5-diamino-uracil (2:6-dihydroxy-4:5-diaminopyrimidine) (see p. 825) by condensation with formic acid:



Xanthine may, of course, be written in the tautomeric forms (a) and (b), just as in the case of uric acid.

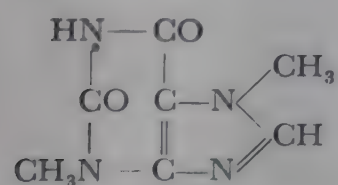
The compound crystallizes well, and is very sparingly soluble in water; it forms salts with alkalis, but also forms a hydrochloride, $\text{C}_5\text{H}_4\text{O}_2\text{N}_4 \cdot \text{HCl}$ with hydrochloric acid, and a nitrate with nitric acid. It gives the murexide reaction.

Xanthines methylated at the nitrogen atom are very important natural products. In the metabolism of nucleic acids in animals, xanthine (likewise hypoxanthine, see p. 828) partly undergoes an enzymic oxidation to uric acid and is thus excreted or further degraded (e.g. in carnivorous animals) to allantoin (see p. 822).



1:3-DIMETHYLBXANTHINE, THEOPHYLLINE, occurs in small quantities in tea leaves. It can be made synthetically, e.g. by Traube's method from dimethylurea and cyanoacetic ester. It forms colourless tablets, m.p. 268° , which dissolve readily in hot water, but with difficulty in cold water.

It has a strong effect on urination, and is used as a diuretic under the name *theocine*.



3:7-DIMETHYLBXANTHINE, THEOBROMINE, is the most important alkaloid of the cocoa bean, in which it occurs up to the extent of 1.8%. Like theophylline it dissolves easily only in hot water. It melts at 351° . Methylation of the silver compound of theobromine gives caffeine (see p. 828).

Theobromine can be prepared technically by a number of processes. It is

most conveniently made, for example, by the further methylation of the readily obtainable 3-methylxanthine.

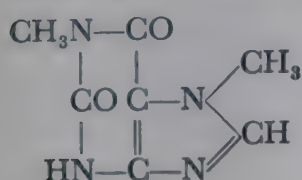
Theobromine has considerable practical importance as a diuretic. It is, however, difficultly soluble in water, and it is frequently used in the form of the double compounds which it forms with salts, and which are often considerably more soluble in water. The following may be mentioned:

Diuretin = sodium compound of theobromine – sodium salicylate

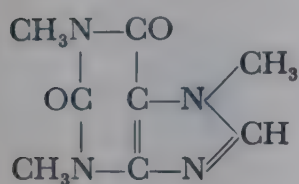
Theolactin = sodium compound of theobromine – sodium lactate

Agurin = sodium compound of theobromine – sodium acetate.

1:7-DIMETHYLXANTHINE, PARAXANTHINE, has been detected in urine and in many animal organs. It melts at 299°, and is difficultly soluble in cold water.



This compound can also be synthesized by Traube's method from monomethylurea.



1:3:7-TRIMETHYLXANTHINE, CAFFEINE (theine). This important purine derivative occurs in different plants, all of which are sources of stimulant beverages. It occurs in coffee beans up to the extent of 1.5%. It was discovered in this source almost simultaneously by Runge, Robiquet, and Pelletier (1820). Dried tea leaves contain a still higher percentage of it (up to 5%), and it also occurs in cola nuts, cacao, and Maté (Paraguay tea).

Its artificial preparation from theophylline, theobromine, and paraxanthine by further methylation has already been mentioned. Technically it is synthesized from uric acid, *via* 8-methylxanthine. The majority of it is obtained, however, from tea dust, and as a by-product in the preparation of caffeine-free coffee.

Caffeine exerts a stimulating action on the heart, for which purpose it is largely used in medicine, and which is also produced when tea and coffee are drunk. It is also a diuretic, which, however, is much more a characteristic of the dimethylxanthines.

1-METHYLXANTHINE and 7-METHYLXANTHINE (HETEROXANTHINE). The occurrence of these compounds in considerable quantities in urine is to be noted. Both compounds are only slightly soluble in water, and can be obtained synthetically.

Hypoxanthine. Hypoxanthine or 6-hydroxypurine (formula, p. 826) is fairly widely distributed in plants and animals. It contributes to the structure of the nucleic acids, and can be obtained from them by hydrolysis.

The most convenient method of preparation is that which starts from trichloropurine (p. 826). Hypoxanthine is obtained from adenine (6-aminopurine) by deamination. This can be brought about by the action of nitrous acid or biologically by an enzymic process (*adenase*).

Hypoxanthine is only slightly soluble in water. It is dissolved by alkalis with salt formation, and likewise by mineral acids. On heating it decomposes without melting.

Adenine, or 6-aminopurine (formula, p. 826), is one of the most widely occurring purine bases. In the combined form it takes part in the structure of the nucleic acids, and can be obtained from them readily by hydrolysis. It is found

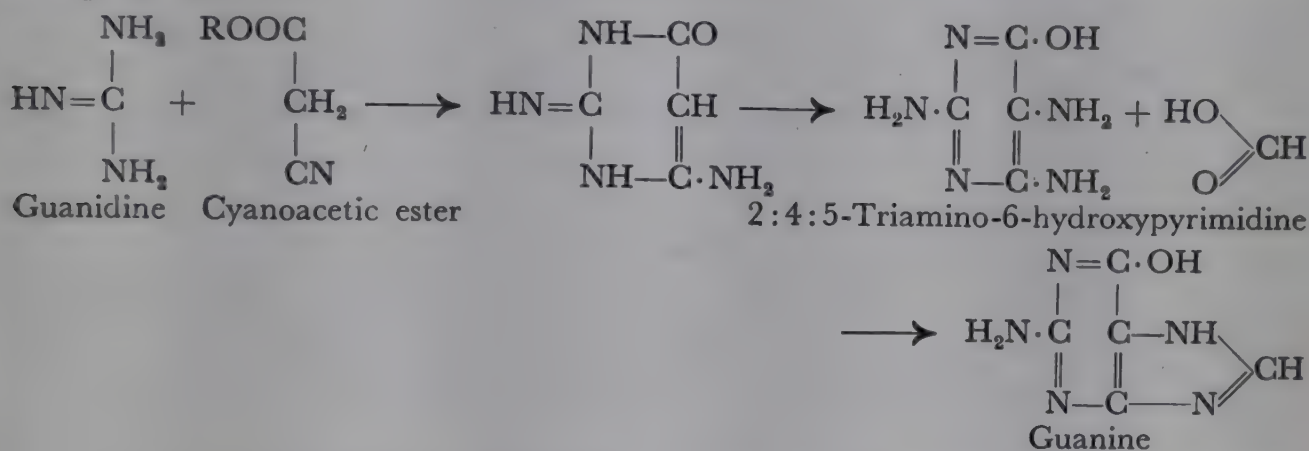
in the free state in numerous plants (tea, sugar-beet, hops, etc.), in fungi (in considerable amounts in yeast), in bacteria, and in animal organs (muscle, placenta, liver), and in urine.

The synthesis from trichloropurine is suitable for the artificial preparation of this substance (p. 826). It has also been obtained on a fairly large scale from tea-extract and molasses.

The compound crystallizes with and without water, and melts at about 360° with decomposition. It may, however, be sublimed at 220°. It is slightly soluble in water, but dissolves readily in mineral acids and in alkalis with salt formation.

Guanine (2-amino-6-hydroxypurine) (formula, p. 826) accompanies adenine in many plants and animal organs. Considerable quantities are found in the scales and skin of fish, reptiles, and amphibia, whose characteristic shiny, iridescent appearance is often due to crystalline guanine. It is also a constituent of nucleic acids, and is set free when these are hydrolysed.

In addition to the synthesis of guanine from uric acid mentioned on p. 826, Traube's method in particular is to be recommended for the preparation of the compound:



In a manner similar to adenine, guanine can be deaminated by enzymes (*guanases*) which have been shown to be present in extracts of animal organs, and in plant embryos. Xanthine is thus formed.

Guanine is almost insoluble in alcohol and water, but it dissolves in acids and alkalis with salt formation.

Isoguanine is 2-hydroxy-6-aminopurine. The seeds of *Croton tiglium* L. contain a D-riboside of isoguanine. *iso*Guanine has also been isolated from insects.

2-AMINO-6:8-DIHYDROXYPURINE occurs along with uric acid and xanthopterin (p.833) in *Ascides*.

Nucleic acids¹

The nucleic acids or polynucleotides are found combined with proteins in the so-called *nucleoproteins*, which are biologically important, integral constituents of the cell nucleus. Their composition is rather complex and variable. Many *types of virus*² belong to the class of nucleoproteins. Their "molecular weights", obtained *via* the sedimentation constants, are very high, those of certain types of vegetable virus lying between 3,000,000 and 18,000,000.

¹ W. JONES, *Nucleic Acids; Their Chemical Properties and Physiological Conduct*, 2nd ed., London. (1920). — P. A. LEVENE and L. W. BASS, *Nucleic acids*, New York, (1931).

² R. DÖRR, CURT HALLAUER, *Handbuch der Virusforschung*, 2d ed., Vienna, (1938).

By total hydrolysis, the nucleic acids furnish *phosphoric acid*, a *sugar*, *pyrimidine*, and *purine compounds*. The sugar of yeast-nucleic acid and that of plants (wheat) is D-ribose (Levene); thymonucleic acid contains D-2-ribodeseose: $\text{CH}_2 \cdot \text{CHOH} \cdot \text{CHOH} \cdot \text{CH}_2 \cdot \text{CHOH}$ (by the term "desoxy-sugar" or "desose"

$\text{CH}_2 \cdot \text{CHOH} \cdot \text{CHOH} \cdot \text{CH}_2 \cdot \text{CHOH}$ is understood a carbohydrate which has a CH_2 -group in place of an alcohol group $-\text{CHOH}-$).

Among the heterocyclic bases isolated as fission products of the nucleic acids are the following pyrimidines: uracil (see p. 819), thymine (see p. 819), cytosine (see p. 819), methylcytosine (see p. 819), and the following purines: hypoxanthine, guanine, xanthine, and adenine. Thymine occurs particularly in animal nucleic acids (thymonucleic acids).

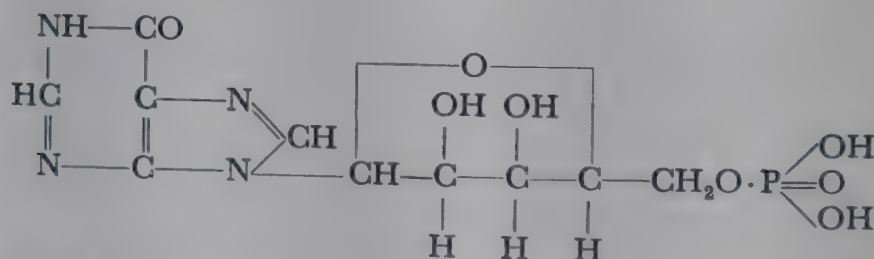
The partial hydrolysis of the nucleic acids has given a somewhat deeper insight into their molecular structure. It has led to two differently constituted types of degradation product:

(a) the nucleotides, or mono-nucleotides (inosinic acid, guanylic acid, adenylic acid), to which may also be added uridylic acid and cytidylic acid, which are composed of phosphoric acid and uridine and cytidine, respectively.

(b) nucleosides: compounds of purine bases and sugars (inosine, guanosine, adenosine) or of pyrimidines and sugars (uridine, cytidine, thymidine).

NUCLEOTIDES (mono-nucleotides).

(a) **INOSINIC ACID.** This is found in meat extract, where it was discovered by Liebig, and where it is probably a secondary product, having been formed from a nucleic acid. Its molecule consists of phosphoric acid, D-ribose, and hypoxanthine, which are linked together as follows:

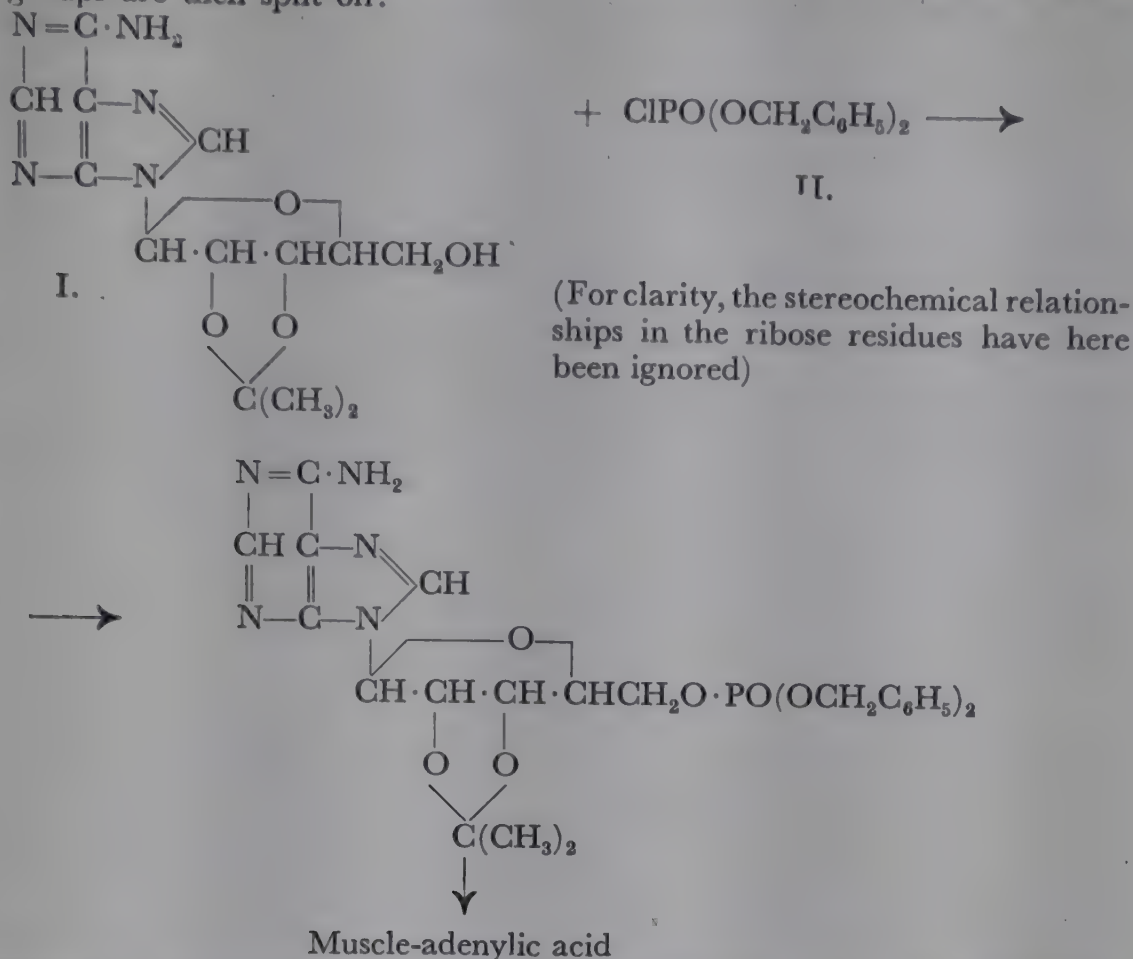


Whilst it is decomposed into its three components by strong hydrolytic attack, it is possible to isolate a hypoxanthine riboside, *inosine* or *hypoxanthosine*, under more moderate conditions. It is also possible to carry out the hydrolysis so as to obtain the ribose phosphate. This has been shown to be a D-ribose-5-phosphoric acid, with a furanose structure.

(b) **MUSCLE-ADENYLIC ACID.** A muscle-adenylic acid, discovered by Embden in muscle, is connected with the degradation of carbohydrates in the animal organism. It arises from an adenosine diphosphate or adenosine triphosphate ($\text{C}_{10}\text{H}_{16}\text{O}_{13}\text{N}_5\text{P}_3$), which on contraction of the muscle are converted into adenylic acid with elimination of one and two moles of phosphoric acid respectively (Lohmann).

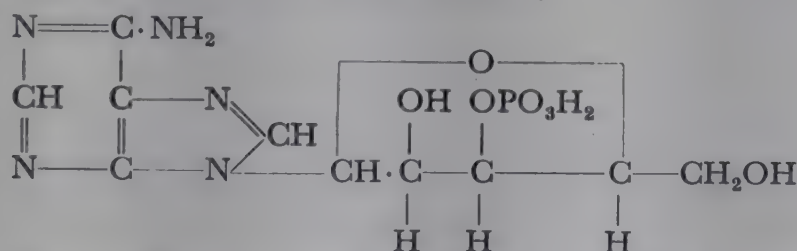
Adenylic acid can be deaminated in the organism, and can be thus converted into the corresponding hydroxypurine derivative, inosinic acid. This straightforward reaction makes clear the constitution of muscle-adenylic acid. Its formula is obtained by replacing the hypoxanthine residue by adenine in the above formula for inosinic acid.

A synthesis of muscle-adenylyc acid has been achieved by A. R. Todd. By means of dibenzyl chlorophosphonate (II), the dibenzyl phosphate group is introduced into 2':3'-isopropylidene-adenosine (I) which is a derivative of adenosine, and the benzyl and isopropylidene groups are then split off:



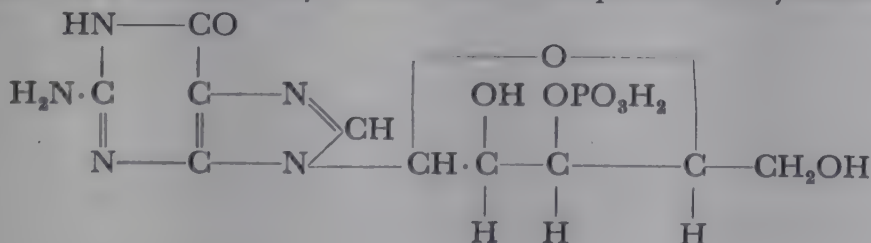
In similar ways the syntheses of adenosine 5'-diphosphate (ADP) and adenosine triphosphate (ATP) have been carried out.

(c) YEAST-ADENYLYC ACID. Careful hydrolysis of yeast-nucleic acid gives rise to yeast-adenylyc acid in addition to the nucleotide guanylyc acid. It has been shown to be different from the adenylyc acid from muscle, the difference being in the position of the phosphoric acid radical, which, in yeast-adenylyc acid, is attached to the third carbon atom of the ribose:



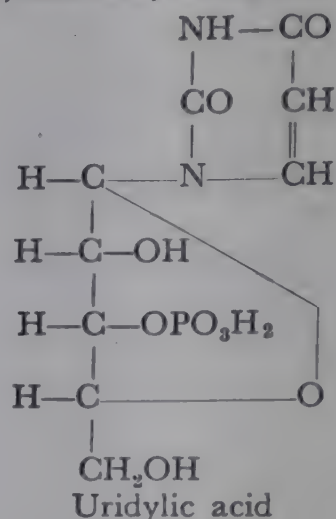
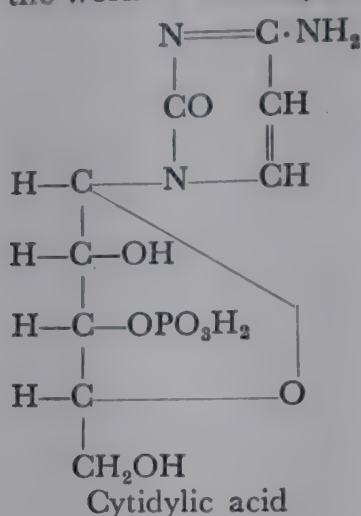
The D-ribose-3-phosphate can be isolated by partial hydrolysis.

(d) GUANYLYC ACID. This mono-nucleotide is also a fission product of yeast-nucleic acid, but also appears to occur in other nucleic acids (thymonucleic acid, pancreas-nucleic acid). It is composed of phosphoric acid, D-ribose, and guanine, linked together in a similar way to the three components in yeast-adenylyc acid:



By partial hydrolysis of guanylic acid, guanine riboside (*guanosine* or *vernine*) which also occurs in plants, can be isolated.

(e) **CYTIDYLIC ACID** and **URIDYLIC ACID**. These two compounds, which correspond in structure to the mono-nucleotides, but contain a cytosine and a uracil nucleus, respectively, in place of a purine base, were obtained by hydrolysis of yeast-nucleic acid with dilute alkali at room temperature. They are therefore integral components of this nucleic acid. Their constitutions have been elucidated as a result of the work of Levene, and Bredereck, and they are given the following formulæ:



As in the case of yeast-adenylic acid and guanylic acid, the phosphoric acid radical in cytidylic acid and uridylic acid is attached at the 3-position of the ribose.

NUCLEOSIDES. This class comprises compounds which are composed of a sugar residue and a pyrimidine or purine base. They are produced directly from nucleic acids under the action of enzymes from lucerne seeds, germinating peas, etc., thus resulting from the above-mentioned mono-nucleotides by elimination of the phosphoric acid radical. Thus, *inosine* is formed from inosinic acid, whilst yeast-adenylic acid and muscle-adenylic acid yield the same *adenosine*, guanylic acid gives *guanosine*, and cytidylic acid and uridylic acid give *cytidine* and *uridine*, respectively, etc. Their formulæ are derivable from those given above for the individual nucleotides. All the nucleosides from yeast-nucleic acid have ribose groups of the furanose type (cf. p. 345).

NUCLEIC ACIDS (poly-nucleotides). Nucleic acids are compounds of high molecular weight, and are made up of numerous mono-nucleotide residues. This is shown, for instance, by their physical properties, which are those expected of colloids.

By the action of enzyme preparations, for example those from the pancreas, and by careful hydrolysis, it is possible to degrade nucleic acids to tetra-nucleotides and other, lower components.

In the best-investigated nucleic acid—that of yeast—adenylic acid, guanylic acid, cytidylic acid, and uridylic acid occur (Levene). Guanylic acid, adenine-, thymine-, and cytosine-nucleotides have been isolated from thymonucleic acid. It is still uncertain how the individual nucleotide residues are linked together. It is possible that the arrangement is not the same in all nucleic acids. The greater stability of thymonucleic acid towards alkalis compared with that of yeast-nucleic acid, for example, suggests that there is a different method of combination.

The linking of the individual mono-nucleotide residues in the nucleic acids appears, however, to take place chiefly by esterification of a hydroxyl group of

the sugar residue of one molecule with a phosphoric acid group of another, and so on:

base—sugar—phosphoric acid

base—sugar—phosphoric acid

base—sugar—phosphoric acid

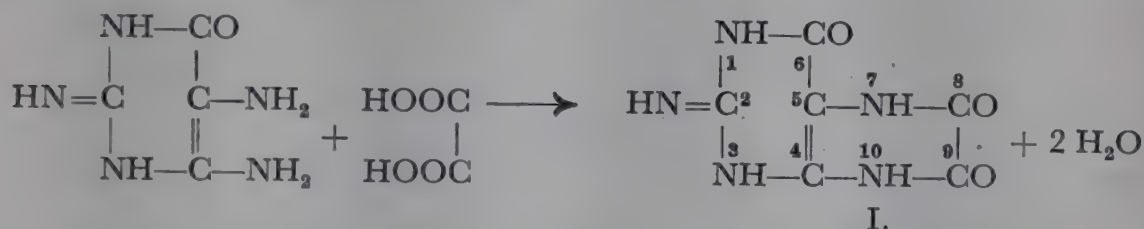
base—sugar—phosphoric acid

Alkaline hydrolysis of yeast-nucleic acid gives guanylic acid and a trinucleotide consisting of uridylic, cytidylic, and adenylic acids. Guanylic acid must therefore stand at the end. Adenylic acid can be split off from the trinucleotide. From such experiments it appears that the order of the components in a part of the molecule of yeast-nucleic acid is: guanylic, uridylic, cytidylic, adenylic acids.

Pterins

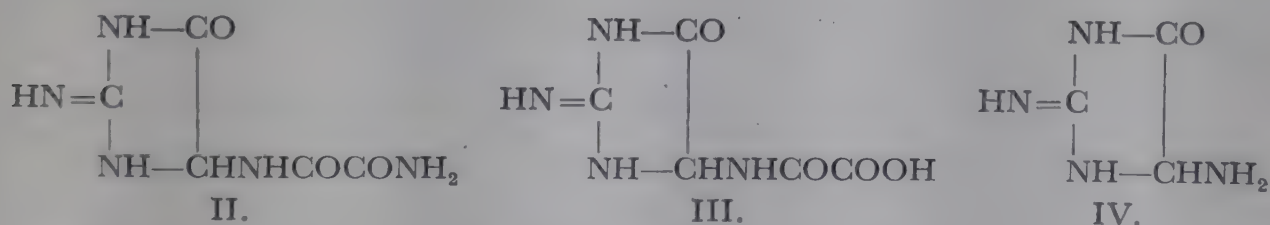
The pterins form a group of compounds, which have been isolated from the wings of butterflies and from other insects, and which are constitutionally related to the purines. They were discovered by H. Wieland, C. Schöpf, and Purrmann.

LEUCOPTERIN, $C_6H_5O_3N_5$, a colourless substance, has the formula I and may be called 2-amino-6:8:9-trihydroxyazinepurine. Its constitution follows from its synthesis; the compound may be prepared by melting together 2:4:5-triamino-6-hydroxypyrimidine and oxalic acid:

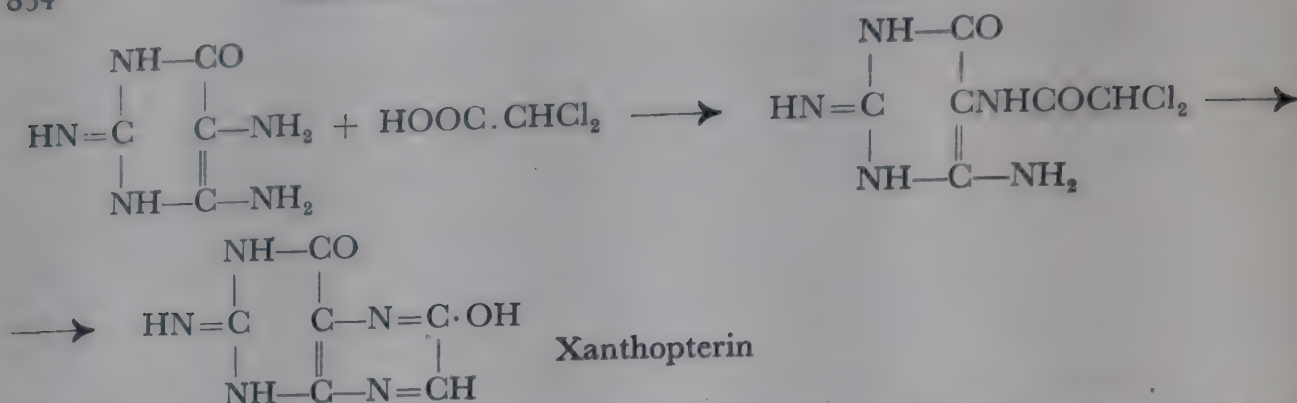


Wieland has proposed the term *pteridine* for the unsubstituted parent compound of the pterins.

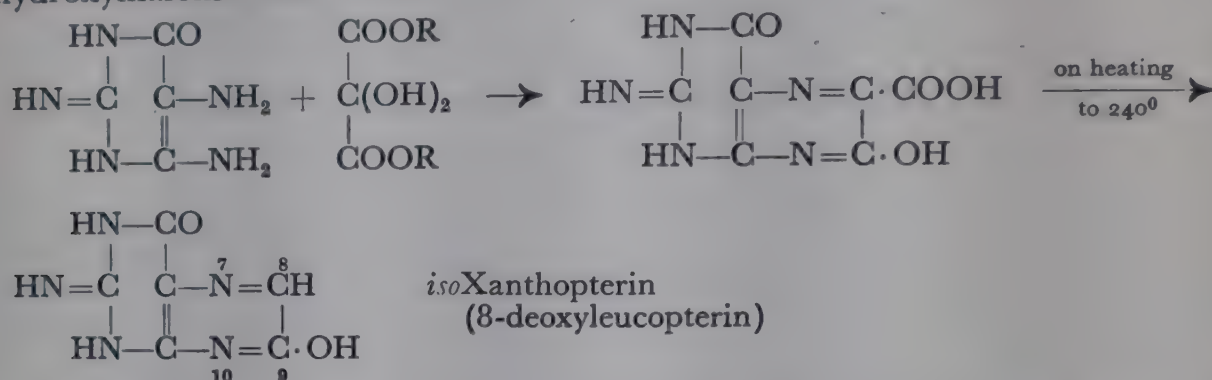
When leucopterin glycol ($C_6H_7O_5N_5$) is acted upon by alkali, 2-imino-hydantoin-oxamide (II) and -oxamic acid (III) are obtained; the latter is converted into 2-imino-5-aminohydantoin (IV) when acted upon by concentrated hydrochloric acid:



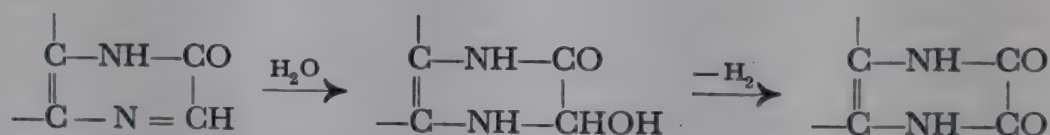
The yellow XANTHOPTERIN, $C_6H_5O_2N_5$, is closely related to leucopterin and may be designated 9-deoxyleucopterin. The compound may be prepared from 2:4:5-triamino-6-hydroxypyrimidine and dichloroacetic acid; the condensation product 2:4-diamino-5-dichloroacetyl-amino-6-hydroxypyrimidine is converted into xanthopterin when treated with silver carbonate or silver acetate:



Isomeric with xanthopterin is *8-deoxyleucopterin*, or *isoxanthopterin*, which occurs, together with leucopterin, in the wings of the cabbage-white butterfly. It has been produced artificially from 2:4:5-triamino-6-hydroxypyrimidine and dihydroxymalonic ester:



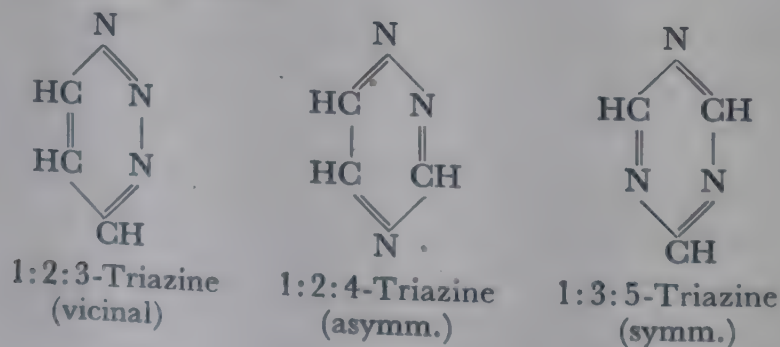
Xanthopterin may be dehydrogenated, with hydrogen peroxide or platinum and oxygen, to leucopterin:



*iso*Xanthopterin and, more readily, xanthopterin may be hydrogenated to colourless dihydro-compounds, which, in alkaline solution, are readily dehydrogenated again by atmospheric oxygen to give the original substances.

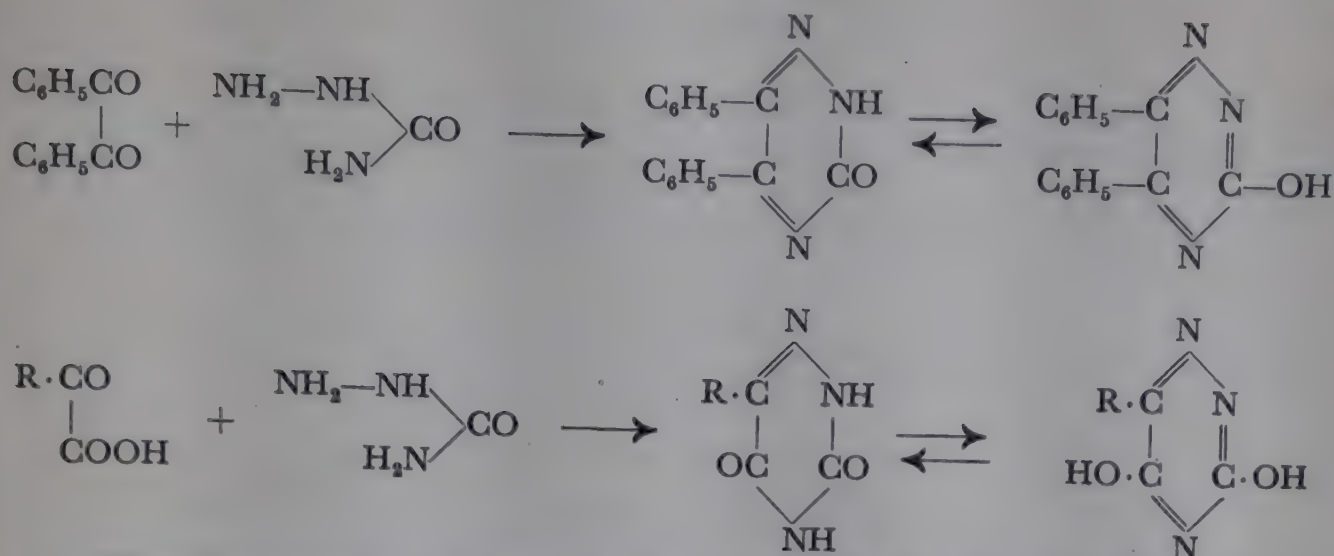
Triazines

There are three possible ways of arranging three nitrogen atoms in a heterocyclic six-membered ring, and these are realized in the vicinal, asymmetrical, and symmetrical triazine systems:



The *1:2:3-triazine* type is known only in condensed ring systems, e.g. in benzotriazine. These compounds are, however, of no particular importance.

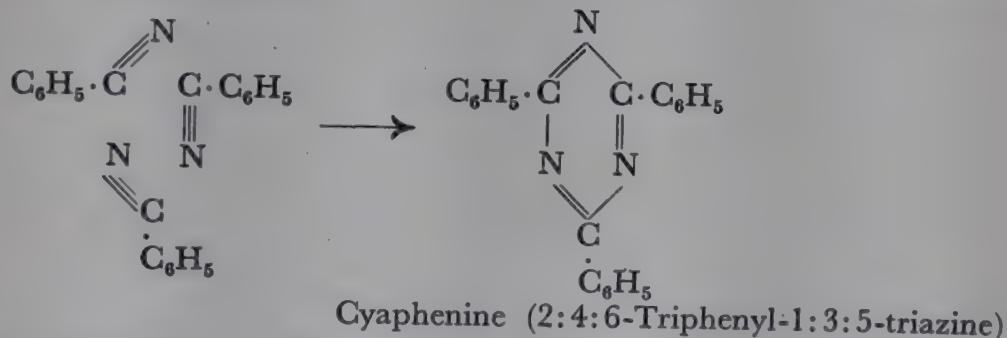
1:2:4-Triazine derivatives are also of little interest. Those containing one or two oxygen atoms are the most easily prepared. They are formed from aromatic diketones, and from α -ketonic acids, on reaction with semicarbazide:



These hydroxytriazines form salts with both bases and acids, but those with the latter are hydrolysed by water.

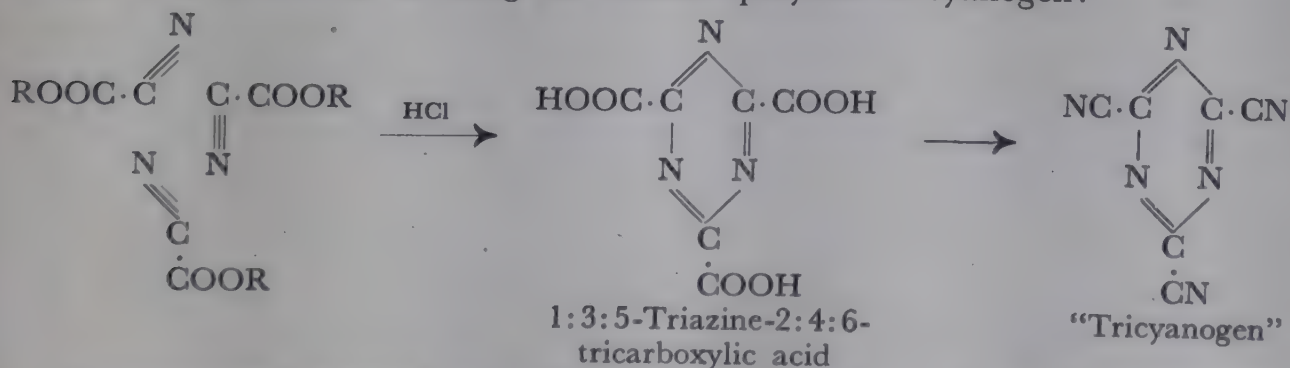
The derivatives of symmetrical, or 1:3:5-triazine form a large class of compounds. Some of them have already been referred to in earlier parts of this book. Thus, cyanuric and isocyanuric acids, cyanuric acid chloride, cyanuric ester, melamine (p. 237), etc., are to be regarded as derivatives of 1:3:5-triazine; hexamethylenetetramine (p. 168) also belongs to this class.

Numerous aromatic derivatives of 1:3:5-triazine can be obtained by polymerization of aromatic nitriles. Whilst aliphatic nitriles usually polymerize to pyrimidine compounds (cyanmethine, etc., p. 819), three molecules of an aromatic nitrile polymerize to a triazine ring under the action of, for example, concentrated sulphuric acid or sodium:



Cyaphenine is a neutral, crystalline compound, insoluble in water and dilute acids.

In a similar way, cyanoformic ester polymerizes to the tricarboxylic acid of 1:3:5-triazine. Ott has prepared the corresponding trinitrile from this, through the amide. It is of interest as being the trimeric polymer of cyanogen:



Tricyanogen is a solid, m.p. 119°. It is hydrolysed even by water to cyanuric acid.

Section II. Alkaloids¹

CHAPTER 63

DEFINITION. OCCURRENCE. ISOLATION

By the term *alkaloids* is now generally understood nitrogen-containing, basic compounds which occur in plants. Their basic character gave rise to the name (alkali-like).

There is, however, a series of simple, basic, nitrogen-containing natural products which, for didactic or other reasons, are usually not considered amongst the alkaloids, but are dealt with elsewhere. To this series belong simple amines, such as methylamine, trimethylamine, and similar compounds, which occur fairly frequently in nature, but which are more properly considered in connection with the other aliphatic amines, as has been done in this book. Also, the aliphatic amino-acids, of which several have a definite basic character, are classed apart from the alkaloids, and these structural units of the proteins, forming a well-defined group, are given a special place in the first part of this book dealing with aliphatic compounds. Finally there are various basic compounds, which are produced by simple reactions from the amino-acids, such as the proteinogenic amines and the betaines, which have already been considered to some extent (p. 295 ff). These latter groups represent the transition from the simple nitrogenous compounds to the true alkaloids. Certain proteinogenic amines, such as tyramine and several betaines (stachydrine, trigonelline, etc.) will be dealt with under the alkaloids.

As the simplest bases are not considered amongst the group of alkaloids, the latter comprises compounds of more or less complicated structure, and they usually have a nitrogen-containing ring system. According to the nature of this nitrogen-containing ring, the alkaloids are classified into sub-groups. There are compounds of the pyrrole and pyrrolidine, pyridine and piperidine, and indole type; quinoline, *isoquinoline*, imidazole, and pyrimidine alkaloids; and then those with condensed ring systems which possess, for example, a pyrrolidine and piperidine, or two pyrrolidine, or one pyrimidine and an imidazole nucleus. A small group of alkaloids must be counted amongst the aromatic amines. Then, finally, there are very many plant bases of which the constitution is wholly or partially unknown.

Plants containing alkaloids occur very widely. Plant bases are, however, only seldom found in cryptogams, gymnosperms, and even monocotyledons, though they are by no means absent altogether. They occur abundantly in dicotyledons, and some families contain a particularly large number of alkaloids, e.g.:

Apocynaceæ (Dog's-bane, quebracho, pereiro bark).

Papaveraceæ (Poppies, opium, celandine).

¹ See E. WINTERSTEIN, *Die Alkaloide*, II. Aufl., bearbeitet von G. Trier, Berlin, (1927-1931). — TH. A. HENRY, *The Plant Alkaloids*, 4th ed., London, (1949). — J. SCHMIDT, *Alkaloide*. (In Abderhalden's Handb. d. biolog. Arbeitsmethoden, I. Abt. Teil 9). — A. LEULIER, *Les Alcaloides*, Fasc. I-III, Paris. (1937).

Papilionaceæ (Pulses, lupins, etc.).

Ranunculaceæ (varieties of *Ranunculus*, aconitum, *Hydrastis canadensis*).

Rubiaceæ (*Cinchona* bark, ipecacuanha).

Solanaceæ (e.g. tobacco, deadly nightshade, potato, thorn apple, etc.).

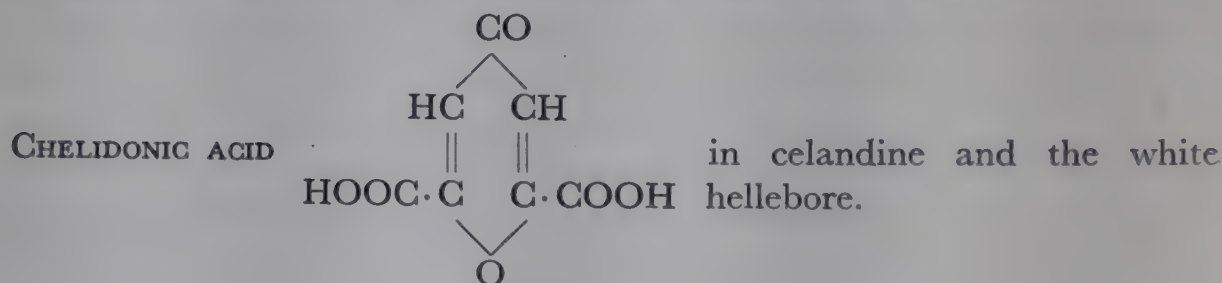
The bases which occur in the same plant are closely related chemically. This fact is important in the determination of their constitution, since it often simplifies the problem, those methods which are used for the determination of the constitution of the principal alkaloid not infrequently also being applicable for the investigation of the subsidiary alkaloids. Simple alkaloids are often found in numerous, botanically unrelated plants; the more complicated (e.g. nicotine, colchicine, cocaine, quinine) are, on the other hand, usually limited to one definite species or genus of plant, and are a distinguishing characteristic of it.

In plants, alkaloids are almost always found combined with acids as salts. While in only isolated cases has it been possible to establish with certainty which acids participate in the combination, yet it is a safe assumption that, as a rule, it is the common simple plants acids such as oxalic, acetic, lactic, malic, tartaric and citric acids which fulfil this function. In some plants rich in alkaloids, however, special acids, characteristic of the particular plant, are involved in the neutralization of the alkaloid, e.g.:

FUMARIC ACID in *Fumaria officinalis*, *Glaucium luteum*, species of *Corydalis*, and *Papaver somniferum*.

CEVADINIC ACID (tiglic acid?), VERATRIC ACID in *Veratrum sabadilla*.

ACONITIC ACID $\text{HOOC} \cdot \text{CH} = \text{C}(\text{COOH}) \cdot \text{CH}_2\text{COOH}$ in species of *Aconitum*.



MECONIC ACID (see p. 806) in opium.

QUINIC ACID (see p. 689) in cinchona bark.

BENZOIC, *p*-HYDROXYBENZOIC, *p*-HYDROXYCINNAMIC, VANILLIC, 2-HYDROXYCINCHONINIC, PHTHALIC, HEMIPINIC, *m*-HEMIPINIC ACIDS, etc. in *Papaver somniferum*.

The amount of alkaloids in plants depends on the place in which they grow, and on the time of year, and can vary greatly. Frequently the occurrence of these compounds is localized in certain parts of the plant, e.g. the seeds, leaves, roots, or bark.

The isolation of the alkaloids usually begins with the treatment of the plant or its acid, aqueous extract with alkalis (ammonia, or caustic alkalis). The plant bases are thus liberated from their salts and can then be separated by extraction with ether, chloroform, etc., or by steam distillation. Occasionally they can also be separated in the form of difficultly soluble salts. The following reagents serve for the precipitation of alkaloids, e.g. phosphotungstic acid, phosphomolybdic acid, picric acid, picrolonic acid (a nitrophenyl-nitro-methylpyrazolone), styphnic acid, anthraquinonesulphonic acid, mercuric salts, potassium bismuth iodide, platinic chloride, iodine-potassium iodide, tannin, potassium ferrocyanide.

Many alkaloids give intense colorations on treatment with sulphuric acid, nitric acid, chromic acid, molybdo-sulphuric acid, ammonia, etc., which are used for the detection of these compounds. They are, however, very rarely sufficiently specific to allow the recognition of an alkaloid without further tests.

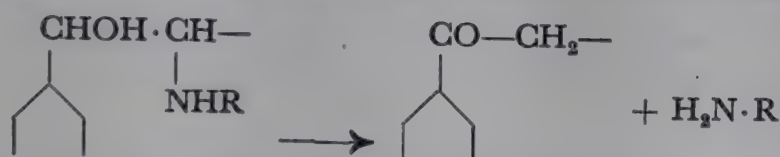
CHAPTER 64

ALKALOIDS OF THE PHENYL-ETHYLAMINE TYPE

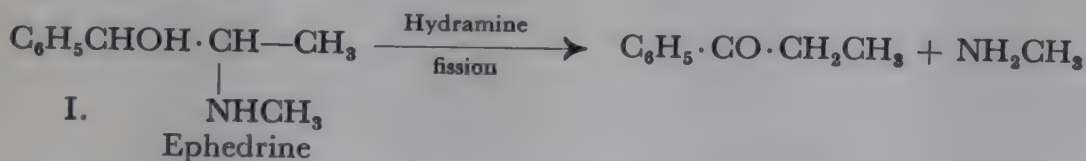
Ephedrine, $C_{10}H_{15}NO$ and **Pseudoephedrine**. Ephedrine was discovered by Nagai in *Ephedra vulgaris*; it occurs there accompanied by various other alkaloids to which it is closely related (*l*-N-methylephedrine, *d*-pseudoephedrine, *d*-N-methylpseudoephedrine, nor-*d*-pseudoephedrine, and *l*-norephedrine).

Ladenburg has shown that it contains a secondary aliphatic amino-group, to which is attached a methyl group, since it gives a nitroso-compound, and since the nitrogen can be eliminated as methylamine on heating with hydrochloric acid. The presence of an alcoholic hydroxyl group can be demonstrated by benzylation, and the presence of the aromatic nucleus by the oxidation of ephedrine to benzoic acid.

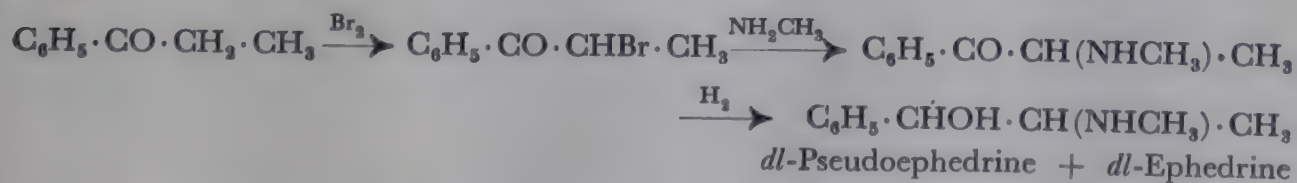
If ephedrine hydrochloride (or pseudoephedrine hydrochloride) is heated it undergoes the so-called "*hydramine fission*", which also takes place with other alkaloids which have a hydroxyl group in the α -position to an aromatic nucleus, and an amino-group in the β -position. The nitrogen from the β -position is removed as an ammonia derivative, and the alcoholic group is converted into a carbonyl group:



In the foregoing case of ephedrine, phenyl ethyl ketone and methylamine are obtained (Schmidt). This fact, together with Ladenburg's observations mentioned above, indicate formula I for ephedrine:

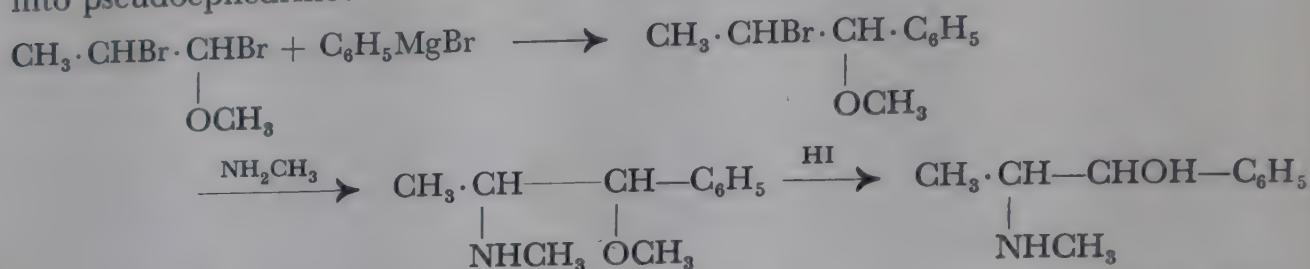


By syntheses of the alkaloid, of which at present there are several, this structural formula is confirmed. One of the first of these syntheses, which gave *dl*-ephedrine, was carried out as follows (Eberhard, improved by Fourneau):

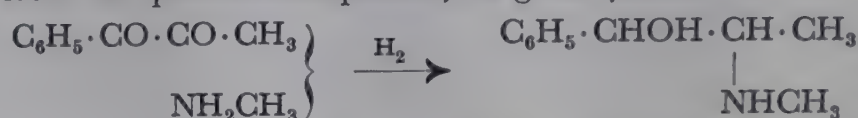


Pseudoephedrine partly isomerizes to ephedrine on long heating with hydrochloric acid.

A second synthesis (Späth) also gave *dl*-pseudoephedrine, which could be resolved into its optically active components by means of the bitartrate. In this synthesis the starting-material was bromopropionaldehyde. It condenses with hydrogen bromide and methyl alcohol giving 1:2-dibromo-1-methoxypropane. The latter reacts with a phenylmagnesium salt giving 1-methoxy-2-bromopropylbenzene. The following scheme shows how this may be subsequently converted into pseudoephedrine:



The most elegant synthesis of ephedrine is that discovered almost simultaneously by Manske and Johnsen and by A. Skita. It consists in the catalytic reduction of phenyl methyl diketone in the presence of methylamine, and gives ephedrine directly, free from the pseudo-compound, in good yield:



Ephedrine and pseudoephedrine are stereoisomerides, but are not enantiomorphs. The two bases have two asymmetric carbon atoms, which requires the existence of two families of antipodes. Ephedrine and pseudoephedrine probably differ in the configurative positions of the OH and H at the first carbon atom of the side chain. If the hydroxyl group of ephedrine is replaced by a hydrogen atom, a base, $\text{CH}_3\text{CH}(\text{NHCH}_3)\text{CH}_2\text{C}_6\text{H}_5$, which is still optically active, is produced. It follows that the second carbon atom of the side chain also contributes to the optical activity of ephedrine.

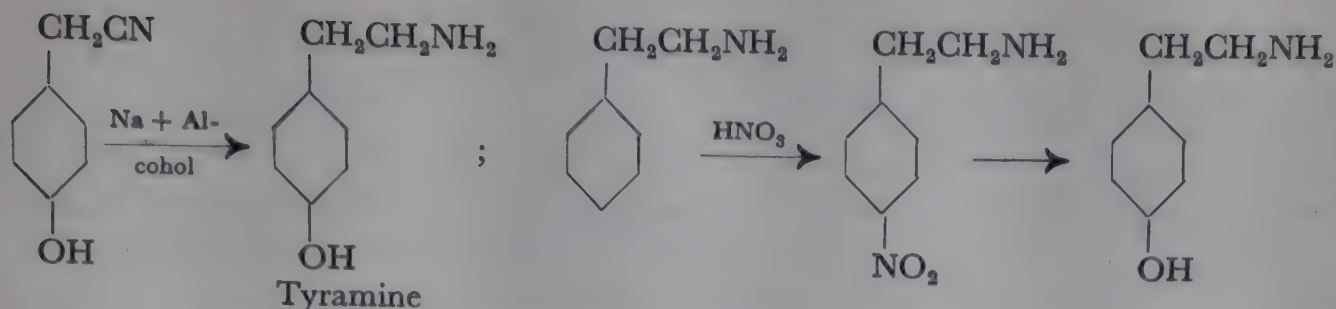
By acetylation and subsequent hydrolysis of *l*-ephedrine, *d*-pseudoephedrine is formed. In the same way a change in the configuration of other optically active alkalines can also be effected.

Ephedrine melts at 40°, and is levorotatory in alcohol, and dextrorotatory in water. The melting point of pseudoephedrine is 118°, $[\alpha]_D = +51.2^\circ$. Both bases have mydriatic properties. Ephedrine has recently been introduced into medicine. It increases the blood pressure, like adrenaline (see p. 462), but has the advantage over the latter that it is also effective if administered orally. It is used, for example, in the treatment of asthma.

Tyramine (p-Hydroxyphenyl-ethylamine) $\text{C}_8\text{H}_{11}\text{NO}$. Tyramine is closely related to the protein amino-acid tyrosine, from which it is produced on heating (best in a high-boiling solvent, such as diphenylamine), or by bacterial decomposition.

For this reason tyramine is often met with in decaying protein, and it is also found in ergot and in mistletoe. Surviving cellular tissue can form tyramine from tyrosine under physiological conditions. The alkaloid belongs, like the two following, to the group of proteinogenic amines, whose connection with the proteins has already been considered on p. 291 ff.

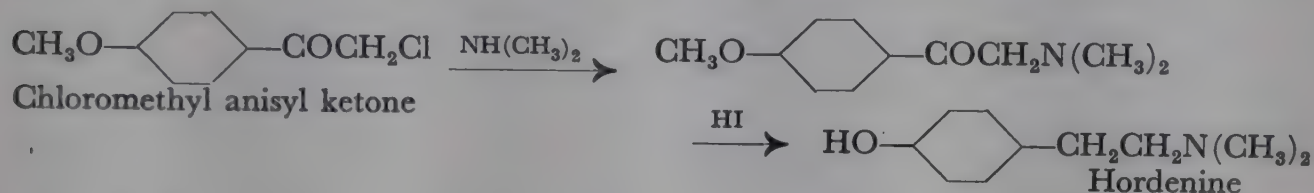
Tyramine has been prepared synthetically by various methods, e.g. from *p*-hydroxyphenyl-acetonitrile by reduction (Barger), and from phenyl-ethylamine and through the *p*-nitro-compound, etc.:



p-Hydroxyphenyl-ethylamine has a boiling point of 179–181° at 8 mm, and crystallizes in leaflets (m.p. 161°). It exerts a strong contracting effect on the uterus, and also contracts the peripheral blood vessels, thus causing an increase in the blood pressure. For these reasons it is used fairly frequently in medicine.

Dipterine. The same relationship exists between *tryptamine* and the protein amino-acid tryptophan as between tyramine and tyrosine. N-Methyltryptamine is found as an alkaloid in *Girgensohnia diptera* BGE. and has been called *dipterine*.

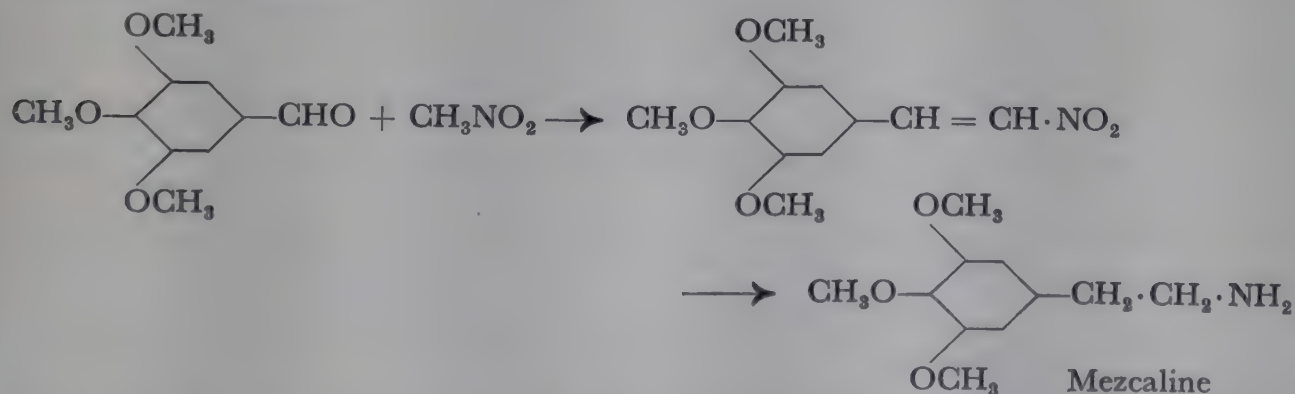
Hordenine, $C_{10}H_{15}NO$. Hordenine, which was discovered by Léger in the embryo of barley, but which also occurs in other plants, e.g. *Anhalonium*, is the N-dimethyl derivative of tyramine. This is indicated by degradation reactions as well as by numerous syntheses. Only one of these can be mentioned:



Hordenine melts at 118°, and boils at 173° at 11 mm. In contrast to tyramine and adrenaline it causes only a slight increase in blood pressure.

Mezcaline, $C_{11}H_{17}NO_3$. A series of alkaloids is found in cacti of the species *Anhalonium*. One of them, hordenine, has already been mentioned. Another is *mezcaline*, which produces in man characteristic disturbance of colour vision, and also lassitude.

By oxidative degradation (potassium permanganate) mezcaline gives gallic acid trimethyl ether. Its constitution follows from its synthesis (Späth). Gallic aldehyde trimethyl ether is condensed with nitromethane, and the trimethoxy- ω -nitrostyrene is reduced:



Mezcaline is an oil; several of its salts (hydrochloride, sulphate, etc.) crystallize well.

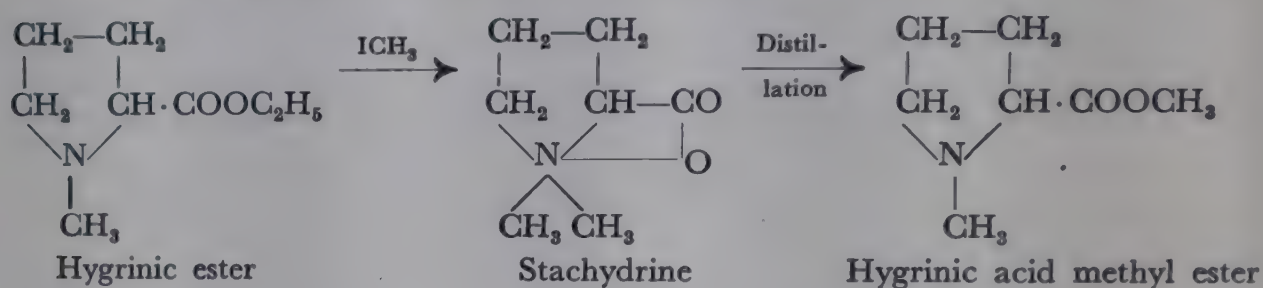
CHAPTER 65

ALKALOIDS WITH A PYRROLE NUCLEUS

The most important alkaloids of this group are the betaines *stachydrine*, *betonidine*, and *turicine*, the alkaloids of the coca leaf, *hygrine* and *cuscohygrine*, and the bases of the tobacco leaf, *nicotine*, etc.

Stachydrine, $C_7H_{13}NO_2 \cdot H_2O$. This simple plant base is related to the protein amino-acid, proline, of which it is the betaine. Stachydrine occurs widely in plants; von Planta and Schulze discovered it in the root tubercles of *Stachys tubrifera*. It is also found, for example, in *Citrus aurantium*, *Betonica officinalis*, alfalfa, and chrysanthemum.

The synthesis of stachydrine by Schulze and Trier consists in the methylation of hygrinic ester or proline:

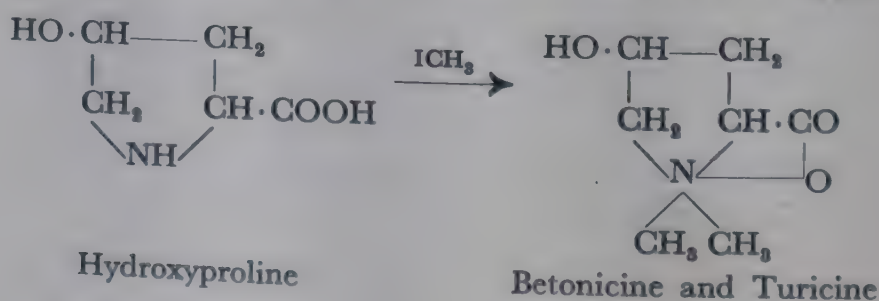


If naturally-occurring L-proline is used as the starting-material, naturally-occurring L-stachydrine ($[\alpha]_D = -26.7^\circ$) is formed. Both compounds therefore have the same configuration.

On distillation, stachydrine rearranges to the methyl ester of hygrinic acid. The compound is readily soluble in water with a neutral reaction; m.p. 235° .

Betonidine and Turicine, $C_7H_{13}NO_3$. These two alkaloids are betaines of hydroxyproline, which is one of the components of proteins. Their difference is a stereochemical one, but they are not enantiomorphous forms. The two asymmetric carbon atoms make possible the existence of more isomerides.

The two betaines are found in *Betonica officinalis*, and *Stachys sylvatica*. They have been obtained synthetically by the methylation of hydroxyproline:

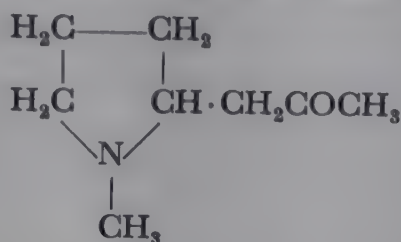


Betonidine decomposes at $243-244^\circ$, $[\alpha]_D^{15} = -36.0^\circ$. Turicine, m.p. 249° , $[\alpha]_D = +36.2^\circ$.

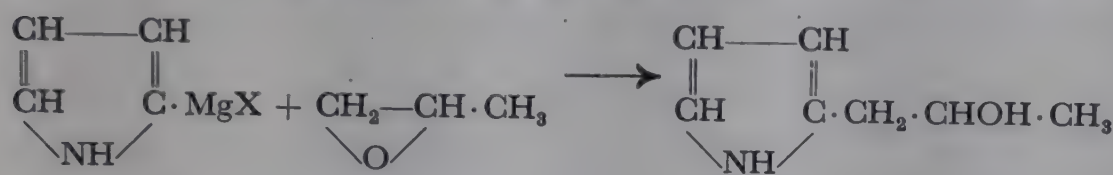
Hygrine, $C_8H_{15}NO$, and **Cuscohygrine**, $C_{13}H_{24}N_2O$. *Hygrine* is an alkaloid of the Peruvian coca leaf, in which it was discovered by Wöhler and Lossen as far back as 1862. The elucidation of its constitution is due chiefly to Liebermann.

Since hygrine forms an oxime it is a ketone. Chromic acid oxidizes the base to *hygrinic acid*, which decomposes into N-methylpyrrolidine and carbon dioxide on heating, and which must therefore be a carboxylic acid of N-methylpyrrolidine. The synthesis of hygrinic acid (Willstätter) showed its constitution to be that of N-methyl- α -pyrrolidinecarboxylic acid (see p. 782).

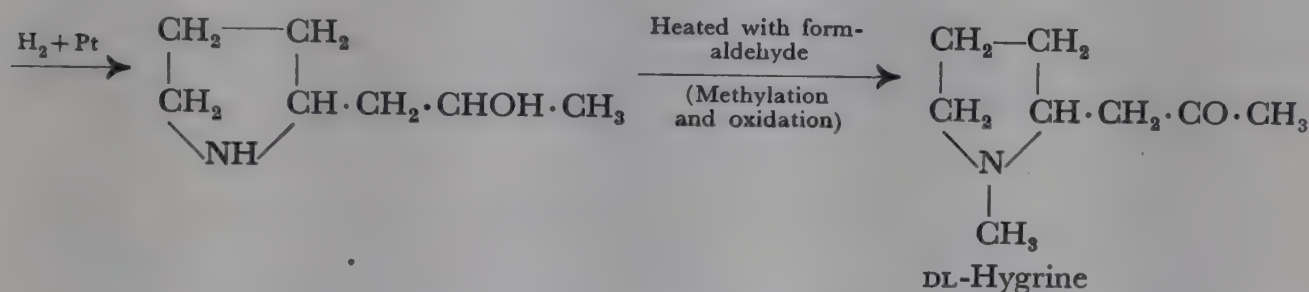
Liebermann has assigned the following formula to hygrine:



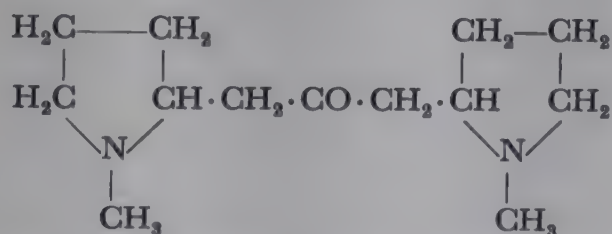
The natural base is slightly laevorotatory, and boils at 193–195°. K. Hess has given the following method for the preparation of racemic hygrine:



Pyrrolemagnesium salt



Cuscohygrine, $\text{C}_{13}\text{H}_{24}\text{N}_2\text{O}$, is found in much greater quantities than hygrine in cusco leaves. It too is decomposed by chromic acid to hygrinic acid. It is a ditertiary base and gives the reactions of the carbonyl group (oxime, semicarbazone, etc.). The formula for cuscohygrine proposed by Liebermann is:



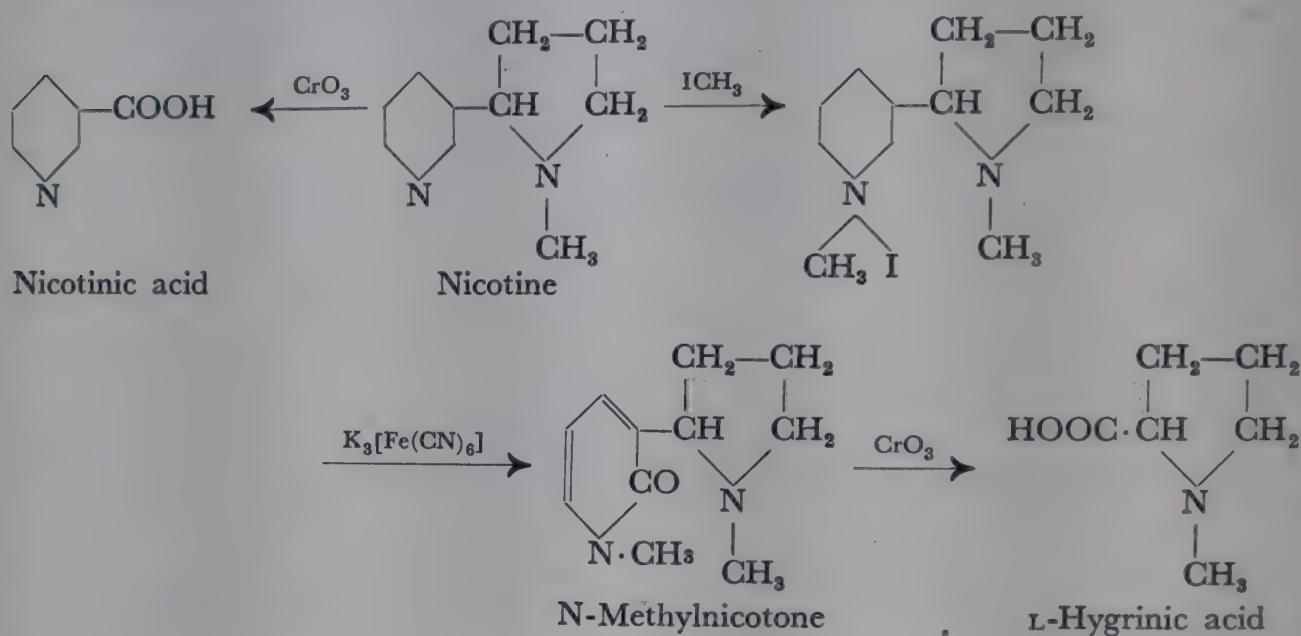
and has been abundantly confirmed; it has very recently been synthesized. It is possible easily to separate cuscohygrine from hygrine by virtue of the fact that the former gives a difficultly soluble nitrate. It boils at 185° at 32 mm.

In the mother liquors from the preparation of cocaine, a substance "hygroline" has been found. It is the secondary alcohol corresponding to hygrine, and is converted into the latter by oxidation with chromic acid.

Nicotine, $\text{C}_{10}\text{H}_{14}\text{N}_2$. The leaves of *Nicotiana tabacum* contain a series of closely related bases. In addition to the chief alkaloid *nicotine*, which was isolated by Posselt and Reimann in 1828, pyrrolidine, N-methylpyrroline, N-methyl-

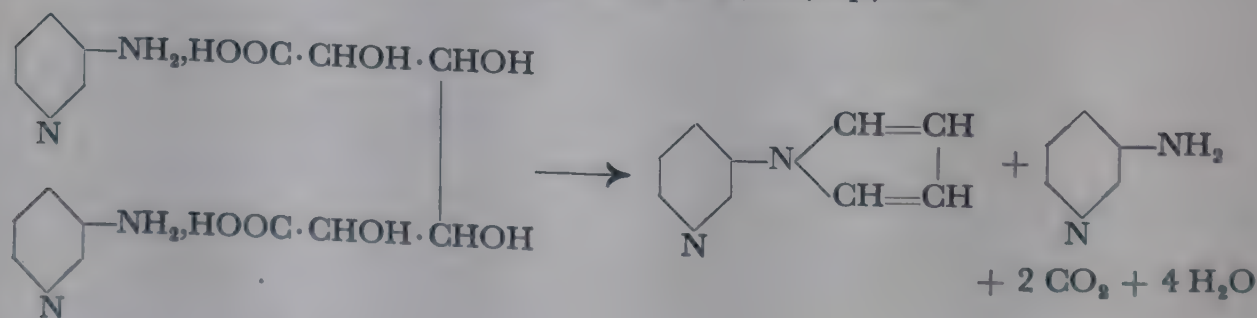
pyrrolidine, *l*-nornicotine, *dl*-nornicotine, nicotyrine, anabasine (p. 853), N-methylanabasine and some other alkaloids are found in this source.

The formula of nicotine, established by Pinner, is based on various degradation reactions. Direct oxidation of the base with chromic acid gives *nicotinic acid*, i.e. β -pyridinecarboxylic acid. One half of the nicotine molecule is thus elucidated. If nicotine py-monomethiodide (py means that the CH_3I is attached at the N of the pyridine ring) is treated with potassium ferricyanide and alkali it is oxidized to N-methylnicotone. Owing to the entry of oxygen into the pyridine residue this becomes more sensitive to chromic acid than the pyrrolidine nucleus; N-methylnicotone can be oxidatively degraded to L-hygrinic acid. It follows that, in nicotine, a pyridine ring is linked through its β -position to the α -position of a N-methylpyrrolidine molecule:

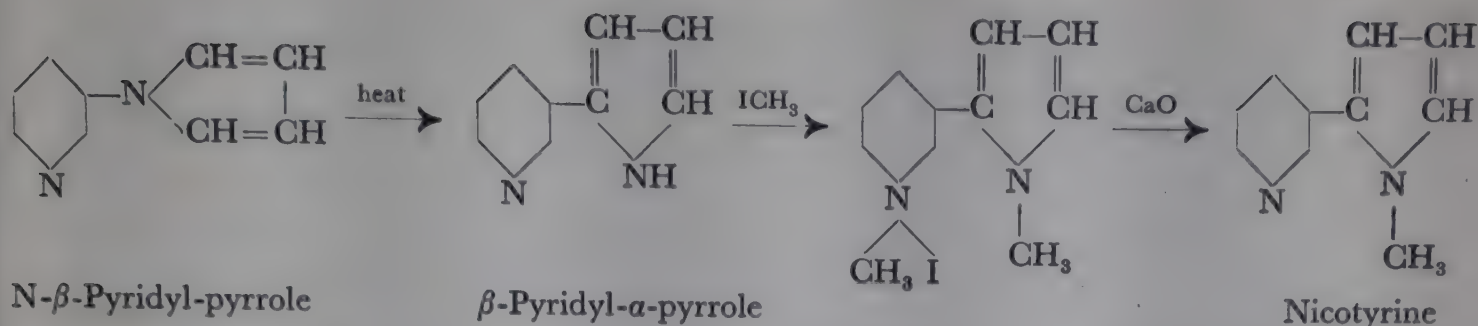


The degradation of natural L-nicotine to L-hygrinic acid shows that the alkaloid has the same configuration as the latter, and as L-stachydrine and L-proline.

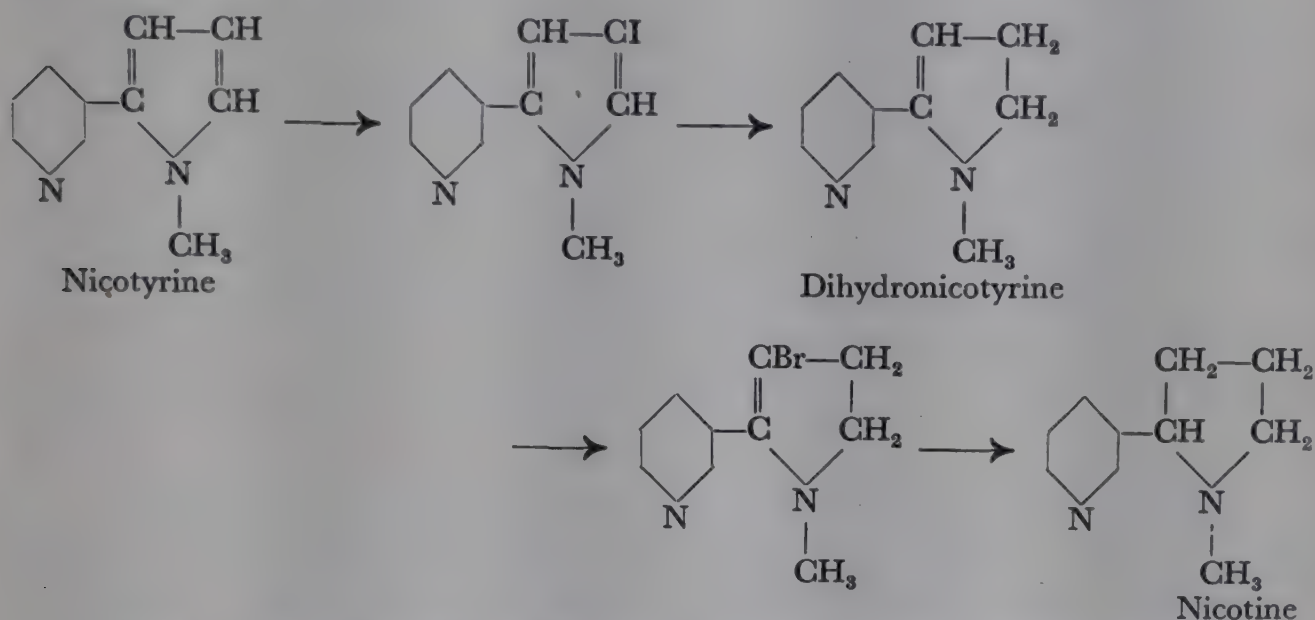
The first total synthesis of nicotine was carried out by A. Pictet. Just as dry-distillation of ammonium mucate gives pyrrole (see p. 768), so heating of the β -aminopyridine salt of mucic acid gives N- β -pyridyl-pyrrole:



Just as the N-alkyl derivatives of pyrrole isomerize on passing through a red-hot tube, so the β -pyridyl compound rearranges into a γ -pyridyl derivative, β -pyridyl- α -pyrrole. By methylation under suitable conditions, the latter was converted into the methiodide of α -(β -pyridyl)-N-methylpyrrole, and this converted by quicklime into nicotyrine [α -(β -pyridyl)-N-methylpyrrole]:

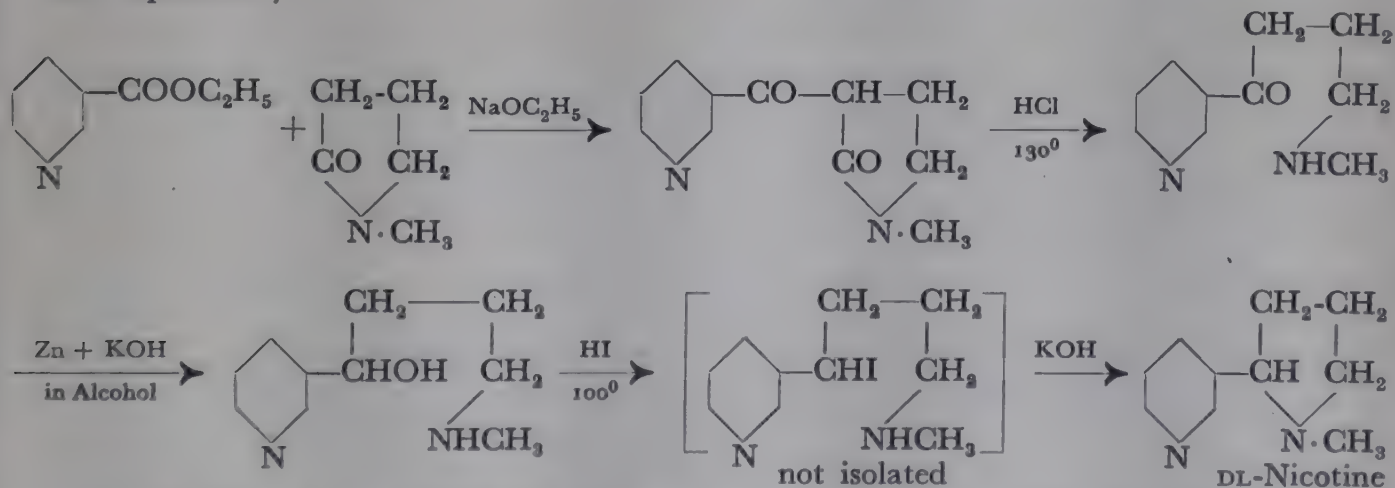


The last stage of the synthesis consists in the reduction of the pyrrole half of nicotyrine. To do this, idonicotyrine was first prepared, and then reduced to dihydronicotyrine. The latter was monobrominated and reduced again. In this way, DL-nicotine is formed, which can be resolved into its enantiomorphic forms by means of the tartrate:



Later it was also found possible to hydrogenate nicotyrine directly to nicotine using a palladium-charcoal catalyst.

More recently a second nicotine synthesis has been put forward by Späth, which starts from nicotinic ester and N-methylpyrrolidone, and takes the following course, which is self-explanatory:



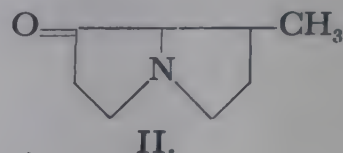
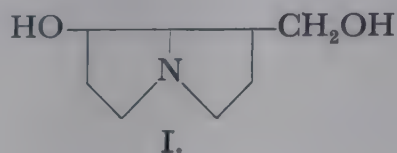
Nicotine is a colourless oil, b.p. 246° , $[\alpha]_D = -168.2^\circ$. Nicotine salts are dextro-rotatory. The alkaloid dissolves freely in water, as well as in most organic solvents.

L-Nicotine stimulates the central and peripheral nerves, and causes increased glandular secretion, contraction of the intestines and, particularly, the blood vessels. It therefore produces a great increase in blood pressure. Atropine (see p. 853) is an antidote, exerting a

paralysing effect on the peripheral nerve endings. The lævorotatory form of nicotine is two to three times more toxic than the dextro-form, and there also seem to be qualitative differences in the effects of the two antipodes.

Monocrotaline. The alkaloid *monocrotaline*, $C_{16}H_{23}O_6N$, from *Crotalaria spectabilis* and *Crotalaria refusa*, is an ester of *retronecine*, $C_8H_{13}O_2N$, an alkamine also occurring in numerous related alkaloids which have been found in about 20 different *Senecio* species. The acids of these retronecine esters are as yet insufficiently investigated; they appear to be in part hydroxy- and keto-acids. Hydrolysis of monocrotaline gave monocrotic acid, $CH_3COCH(CH_3) \cdot CH(CH_3)COOH$, which, however, appears to have been formed with elimination of CO_2 .

The constitution of the basic fission product, retronecine, has been elucidated by the degradative and synthetic work of Roger Adams. It is a pyrrolidine derivative of the structure I.



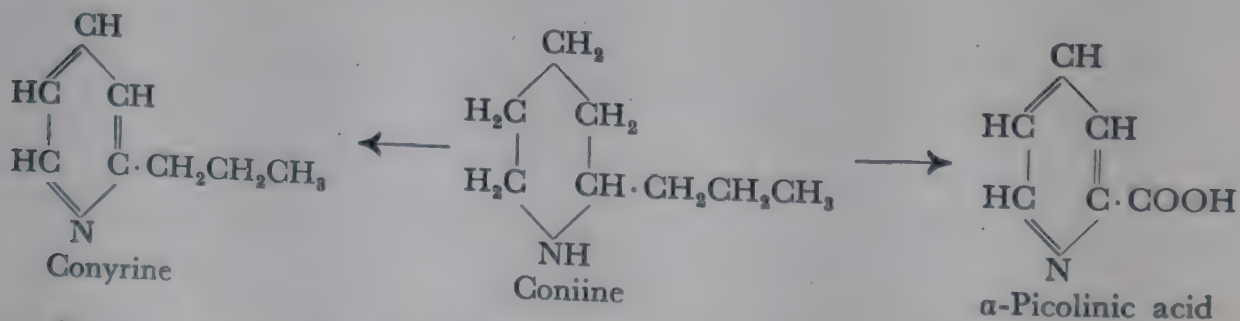
A degradation product of this base, retronecanone (II), has been prepared synthetically in an optically active form.

CHAPTER 66. PYRIDINE ALKALOIDS

1. Hemlock alkaloids

Hemlock (*Conium maculatum*) contains a series of related alkaloids, viz. coniine, N-methylconiine, γ -coniceine, conhydrine, etc. The fruit is particularly rich in these bases, which chiefly occur combined with malic and caffeic acids.

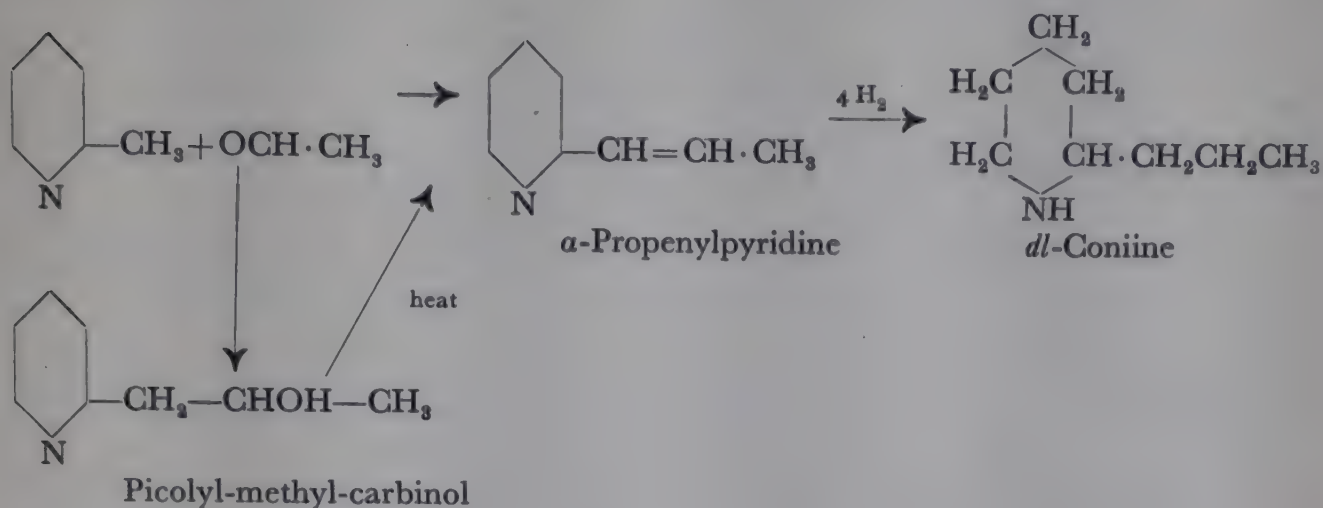
Coniine, $C_8H_{17}N$. By mild dehydrogenation of coniine, e.g. by heating with silver acetate or by the distillation of its hydrochloride with zinc dust, *conyrine*, α -propylpyridine is formed. Stronger oxidizing agents degrade the base to pyridine- α -carboxylic acid, α -picolinic acid. The constitution of coniine is therefore that of α -propylpiperidine:



Various reactions of coniine which take place with disintegration of the ring, and give rise to derivatives of *n*-octane, confirm this formulation. Thus, it is reduced by hydriodic acid to *n*-octane. Its N-benzoyl compound can be broken down by potassium permanganate to δ -aminocaprylic acid and by phosphorus pentachloride to 1:5-dichloro-*n*-octane.

The first synthesis of an alkaloid ever accomplished was that of coniine by Ladenburg (1886). α -Picoline was the starting material. It condenses with acetaldehyde at low temperatures to picolyl-methyl-carbinol, and at higher temperatures

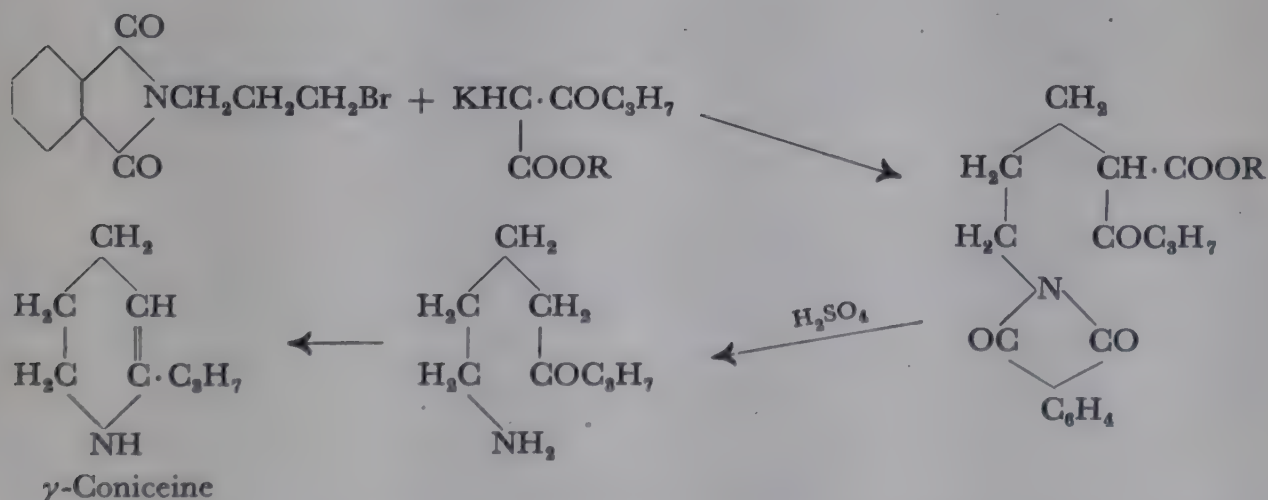
directly to α -propenylpyridine. On reduction, propenylpyridine is converted into *dl*-coniine, which can be resolved into its optically active forms by means of tartaric acid:



Natural coniine is dextrorotatory, $[\alpha]_D = +15.7^\circ$. The oily base (b.p. 166°) is only slightly soluble in water, but readily soluble in alcohol. It is very poisonous, causing central paralysis and paralysis of the motor nerve endings and muscles. Large doses are fatal, causing cessation of respiration.

N-METHYLCONIINE is found in species of hemlock and apparently in both the lævo- and dextrorotatory forms. $[\alpha]_D = 81.9^\circ$; b.p. 175.6° . The compound has been obtained synthetically, e.g. by the methylation of coniine.

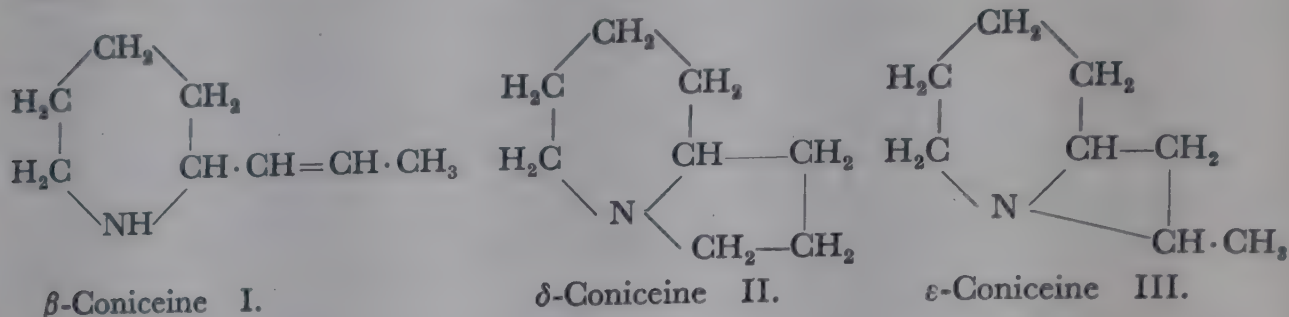
γ -Coniceine, $\text{C}_8\text{H}_{15}\text{N}$. From the fact that it can be reduced to *dl*-coniine, and can readily be converted into conyryne (distillation with zinc dust), γ -coniceine is recognized as an α -propyl-tetrahydropyridine. The position of the double bond follows from the optical inactivity of γ -coniceine and its character as a secondary base (α -propyl- Δ^a -tetrahydropyridine). The Gabriel synthesis of γ -coniceine is based on the condensation of phthalimido-bromopropane with potassium butyryl-acetic ester, and hydrolysis of the phthalimidopropyl-butyrylacetic ester:



Amongst other synthetic methods of preparing γ -coniceine may be mentioned the elimination of water from conhydrine (see below), during which process β -coniceine (see below) is formed as a second product.

The boiling point of γ -coniceine is 173–174°. It is a powerful poison.

Several isomerides of γ -coniceine have been obtained synthetically. β -CONICEINE is regarded as being an α -propenylpiperidine (I):

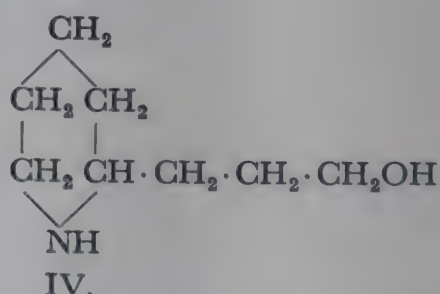
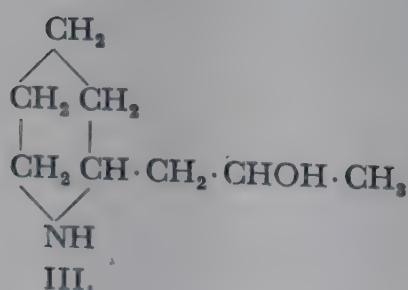
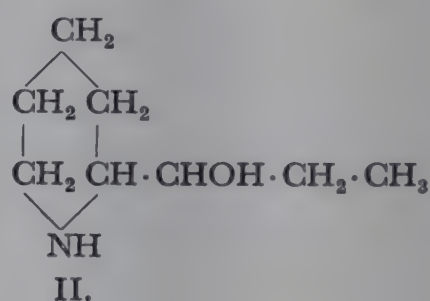
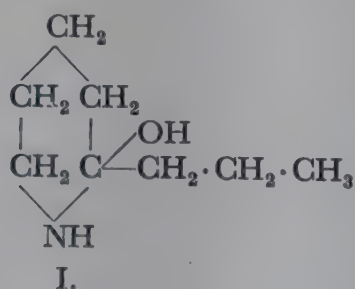


It is obtained together with γ -coniceine on heating conhydrine with phosphorus pentoxide.

δ -CONICEINE (piperolidine) (II) is one of the products obtained from N-bromoconiine by elimination of hydrogen bromide with sulphuric acid.

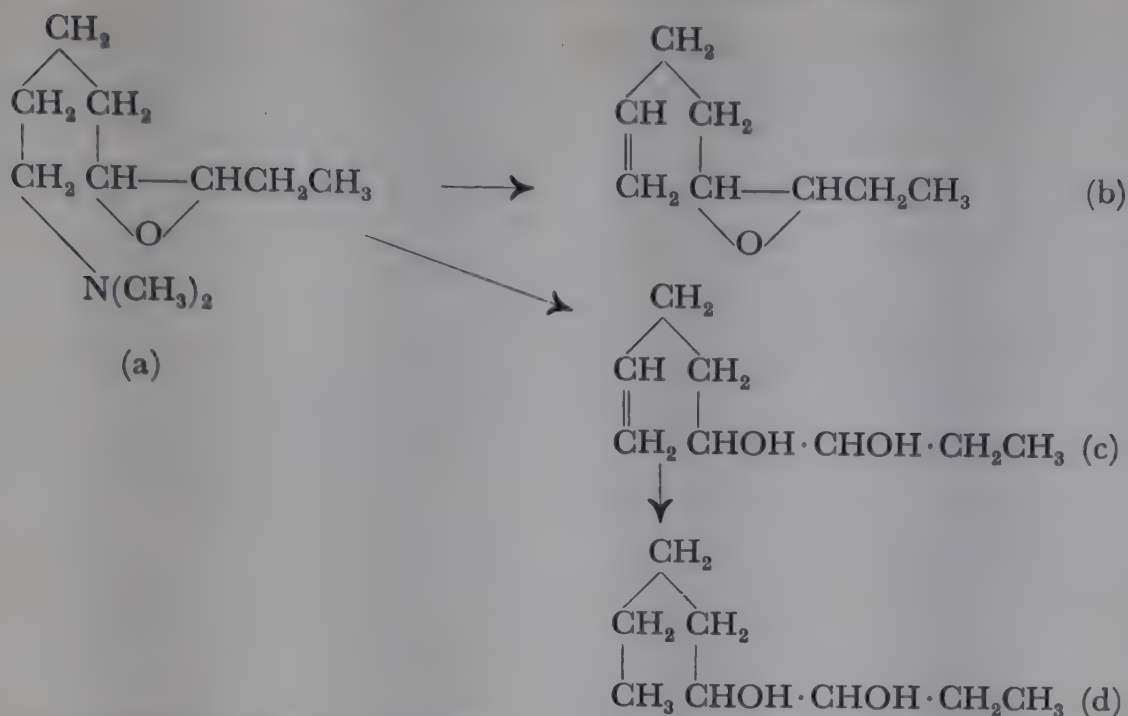
ϵ -CONICEINE (2-methylconidine) (III). A mixture of stereoisomeric bases having the structure of ϵ -coniceine is obtained from conhydrine by the action of fuming hydriodic acid.

Conhydrine, $C_8H_{17}NO$. This hemlock alkaloid is a secondary base and contains an alcoholic hydroxyl group. On oxidation it gives *l*-pipecolinic acid. Conhydrine must, therefore, be a hydroxyconiine, which has the alcoholic group in the side chain. Of the four possible formulæ:



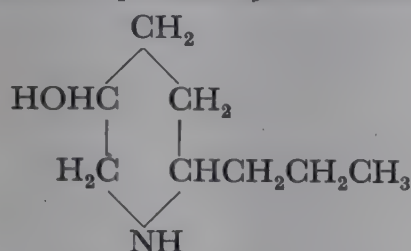
the first is excluded by the production of pipecolinic acid on oxidation and also because the *coniceines* formed by elimination of water from conhydrine are optically active. From IV a piperidylpropionic acid would be formed by oxidation and this is not the case. Formulæ II and III remain.

It has been possible to decide between these two by the Hofmann degradation of the base. By methylation and subsequent action of silver oxide, conhydrinemethine (a) was produced, which, on further exhaustive methylation, gave the compounds (b) and (c). (c) was decomposed to propionaldehyde and succinic acid, and its hydrogenation product (d) to valeric acid on oxidative degradation. It follows from these reactions that conhydrine has the formula II:



In contrast to the oxygen-free hemlock bases, conhydrine is solid at room temperature. It melts at 120–121°, and boils at 225–226°.

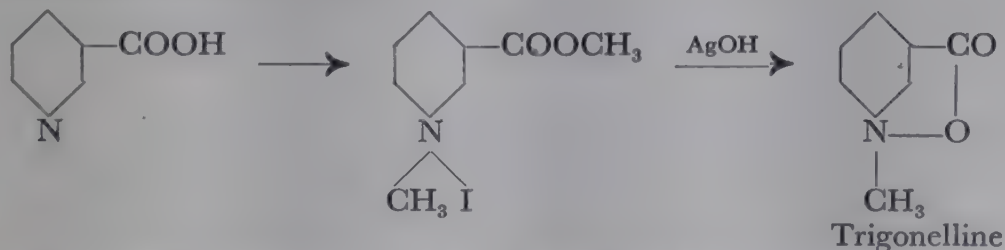
According to Späth, the isomeric *pseudoconhydrine* has the structure:



2. Trigonelline, $C_7H_7NO_2$

In trigonelline we meet again a simple betaine, that of N-methylnicotinic acid, which is widely distributed in nature. It is found, for example, in the seeds of fenugreek (*Trigonella fænum græcum* L.), in peas and various kinds of grain, in *Strophanthus* seeds, etc., and it also occurs normally in human urine.

The constitution of trigonelline is arrived at from the fact that when heated with hydrochloric acid it breaks down into methyl chloride and nicotinic acid. Moreover, it can be synthesized by the methylation of nicotinic acid by means of methyl iodide and silver oxide:



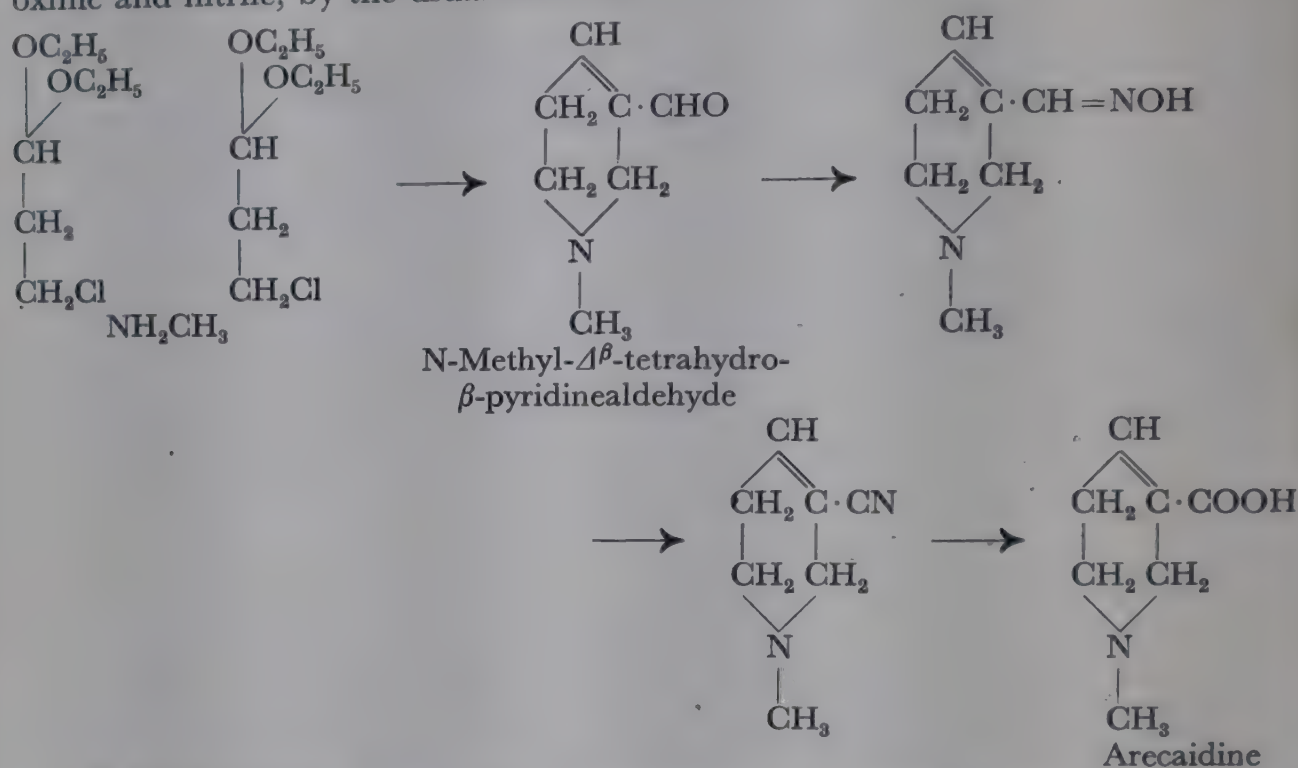
Trigonelline, which crystallizes well, is readily soluble in water. The solution reacts neutral.

3. Areca Alkaloids

The betel nut, the fruit of *Areca catechu*, contains various alkaloids combined with tannic acid. Jahns discovered arecaidine, arecoline, and guvacine in this source, and later guvacoline and arecolidine were also found.

Arecaidine, $C_7H_{11}NO_2$, and **Arecoline**, $C_8H_{13}NO_2$. *Arecaidine* is reduced by alcohol and sodium to N-methyl-hexahydronicotinic acid (N-methyl-nipecotinic acid). This reaction, together with the composition of the alkaloid, indicates the formula of a N-methyl-tetrahydronicotinic acid. The position of the double bond was determined by the synthesis of arecaidine (Wohl and Johnson):

This begins with the condensation of two molecules of β -chloropropionacetal and methylamine to methylimino-dipropionacetal. If the latter is then heated with hydrochloric acid, hydrolysis to the dialdehyde occurs, and then intramolecular elimination of water. N-Methyl- Δ^{β} -tetrahydro- β -pyridinealdehyde is formed which can be converted into the carboxylic acid, arecaidine, through the oxime and nitrile, by the usual reactions:

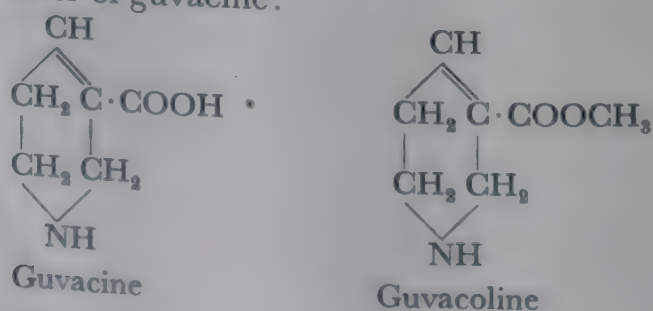


A new synthesis of arecaidine depends upon heating N-methyl-4-hydroxypiperidine-3-carboxylic acid or its esters with halogen hydracids and glacial acetic acid. Elimination of water occurs and arecaidine is formed.

Esterification of arecaidine with methyl alcohol gives rise to *arecoline*, which is therefore arecaidine methyl ester.

Arecaidine melts when anhydrous at 232° , and dissolves easily in water, but with difficulty in organic solvents. Arecoline is a strongly basic oil (b.p. 209°). It is the principal alkaloid of the betel nut and is distinguished from the other betel nut bases by its toxicity (myotic; causes salivation).

Guvacine, $C_6H_9NO_2$, and **Guvacoline**, $C_7H_{11}NO_2$. Guvacine differs from arecaidine in not having a methyl group attached to the nitrogen atom. It is thus norarecaidine. Guvacoline bears the same relationship to arecoline. Guvacoline is the methyl ester of guvacine:



This constitution for guvacine is supported by the fact that the alkaloid can be converted by methylation at the nitrogen atom into arecaidine, and also by its identity with synthetic Δ^{β} -tetrahydronicotinic acid.

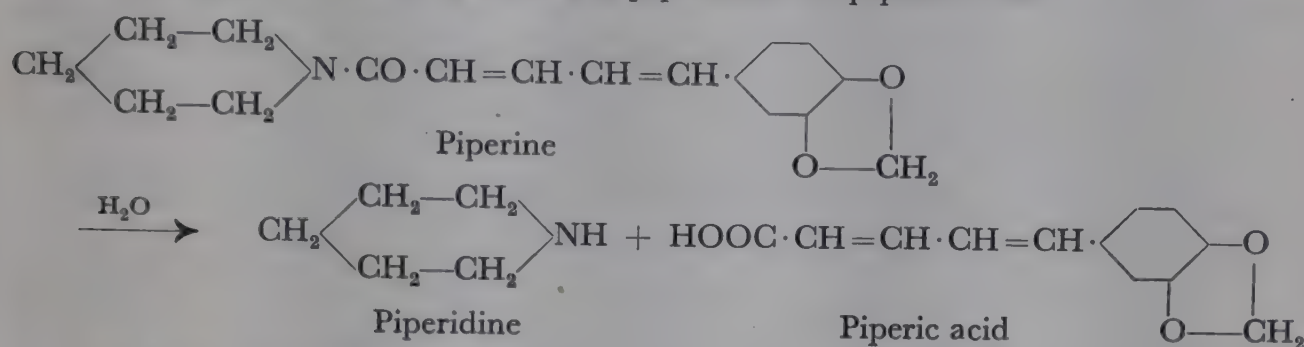
The melting point of guvacine is 293°. Guvacoline is an oil.

4. Alkaloids of pepper

In addition to traces of simpler bases (methyldpyrroline) the fruits of various kinds of pepper (*Piper nigrum*, *Piper longum*, etc.) contain principally the alkaloid **piperine**, $C_{17}H_{19}NO_3$.

This is a well-crystallized compound, very difficultly soluble in water (m.p. 128–129°). Its solution reacts neutral to litmus. It is the chief product responsible for the sharp taste of pepper.

Acid hydrolysis of piperine decomposes it into piperidine (see p. 810) and piperic acid (see p. 543). It is thus a piperidide of piperic acid:



As both piperidine and piperic acid can be synthesized and combined to form piperine, the alkaloid has been totally synthesized.

A second bitter-tasting principle, *chavicine* (Ott) occurs in pepper resin. This too is a piperidide of an unsaturated acid, *chavicinic acid*.

Chavicinic acid is a geometrical isomeride of piperic acid. In consequence of the presence of two double bonds there are four *cis-trans* isomeric forms possible, of which all are known, and of which the configurations have been elucidated. The four stereoisomeric acids have the following configurations.

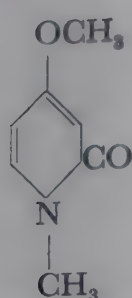
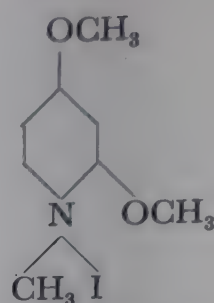
Piperic acid	α -trans	γ -trans
isoPiperic acid	α -cis	γ -trans
Chavicinic acid	α -cis	γ -cis
isoChavicinic acid	α -trans	γ -cis

The most unstable of these isomerides is *isochavicinic acid* (Lohaus).

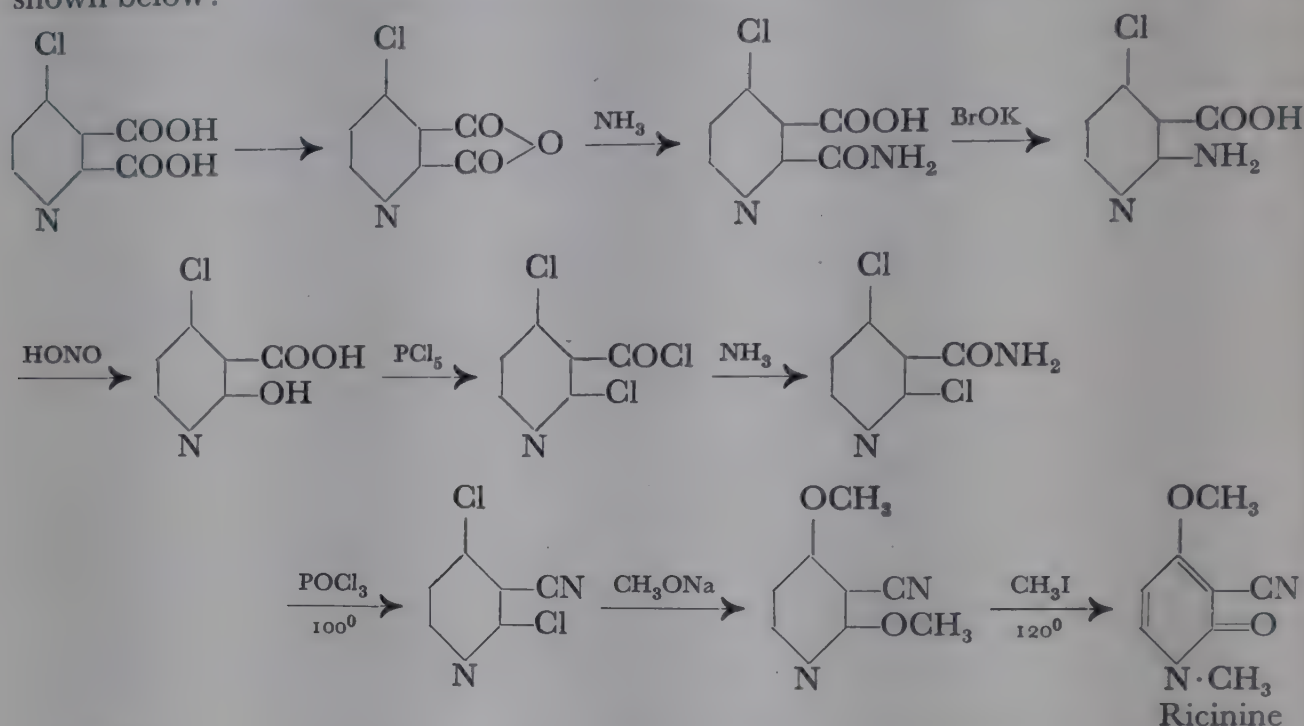
5. Ricinine, Lobeline, Anabesine

In the poisonous seeds of *Ricinus communis* L. there is, in addition to a high-molecular toxin of unknown nature (ricine), an alkaloid of the pyridine series, **ricinine**, $C_8H_8N_2O_2$, which was discovered by Tuson in 1864, and whose constitution has been fully elucidated by the work of Maquenne, and in more recent times by that of Späth.

The alkaloid is decomposed by sulphuric acid with the formation of N-methyl- γ -methoxy- α -pyridone, along with ammonia and carbon dioxide. This compound can be prepared from α,γ -dimethoxypyridine methiodide by removal of methyl iodide:

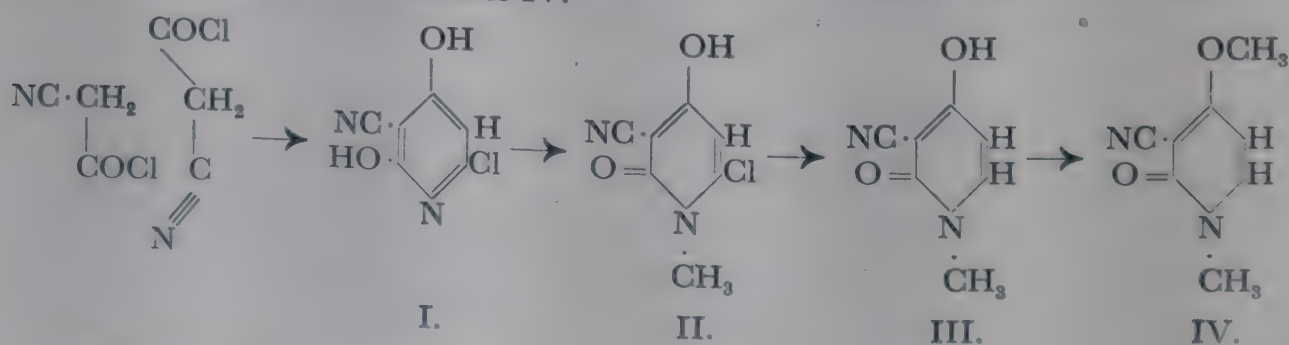
N-Methyl- γ -methoxy- α -pyridone α,γ -Dimethoxypyridine methiodide

The constitution of ricinine itself has been established by synthesis (Späth). This starts from 4-chloropyridine-2:3-dicarboxylic acid, and takes the course shown below:



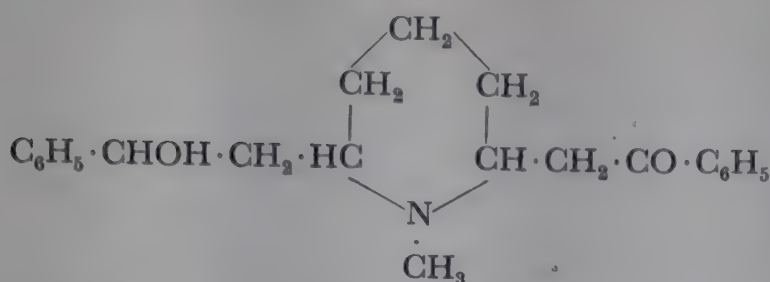
Ricinine is thus N-methyl-3-cyano-4-methoxy-2-pyridone. It is optically inactive, melts at 201° , can be sublimed *in vacuo*, and has an intensely bitter taste. Its aqueous solution reacts neutral.

A second simple synthesis of ricinine has been successfully carried out by G. Schroeter. Cyanacetyl chloride polymerizes spontaneously on standing to give the product I (the nitrile of 2:4-dihydroxy-6-chloro-3-nicotinic acid). This can be methylated to chlororicininic acid II. The chlorine of the latter is removed by reduction, and the ricininic acid III is further methylated to ricinine IV.



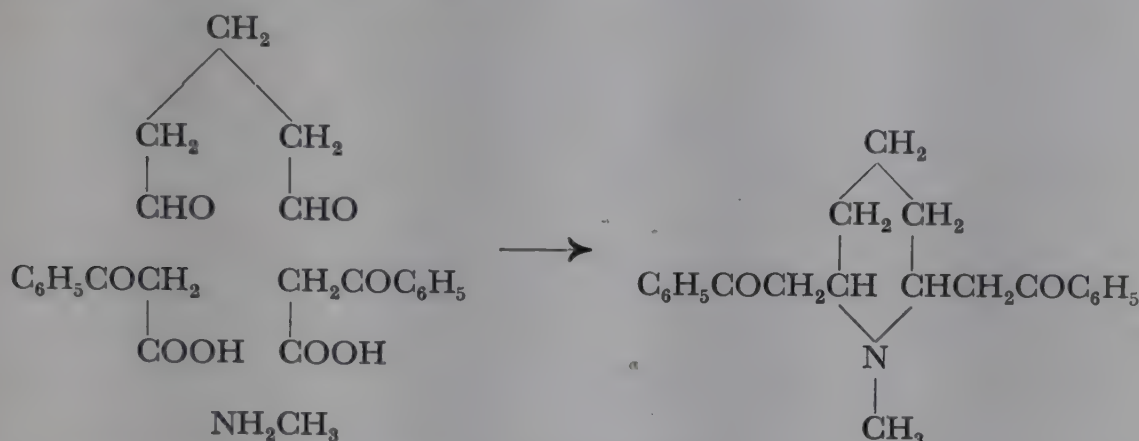
For isopelletierine, see p. 864.

Lobeline, $C_{22}H_{27}NO_2$, is a base from *Lobelia inflata*. Its constitution has recently been elucidated by Wieland. It is a piperidine derivative of the following formula:



The alkaloid, which stimulates the respiratory centres, is at present quite often used in medicine for the relief of breathing difficulties. In the lobelia plant there are also various other alkaloids related to lobeline.

By oxidation of the secondary alcohol group in lobeline the base is converted into *lobelanine*, which can be synthesized relatively simply from glutaric dialdehyde, benzoylacetic acid, and methylamine:



Anabasine, an alkaloid from *Anabasis aphylla* is a α -(β -pyridyl)-piperidine. It also occurs in tobacco. It differs in constitution from nicotine by the replacement of the N-methylpyrrolidine ring by a piperidine moiety.

CHAPTER 67

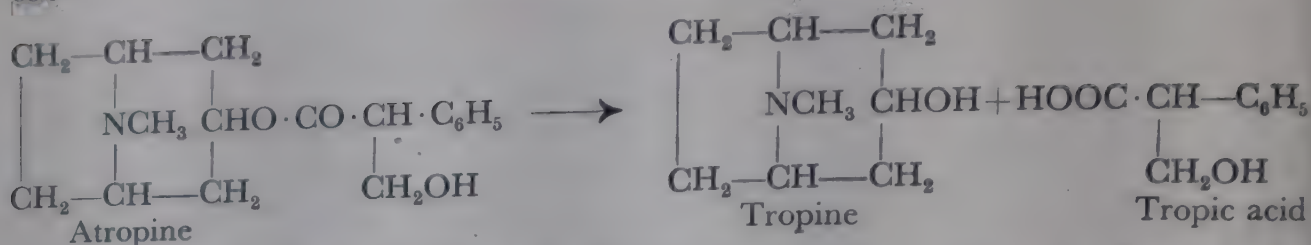
ALKALOIDS WITH CONDENSED PYRROLIDINE AND PIPERIDINE RINGS

1. Atropine group

Several constitutionally related alkaloids occur in a series of different *Solanaceae*, especially in *Atropa belladonna* (deadly nightshade), *Hyoscyamus niger* (henbane), *Datura stramonium* (thorn-apple), *Scopolia carniolica*, etc. The most important and best known of these are:

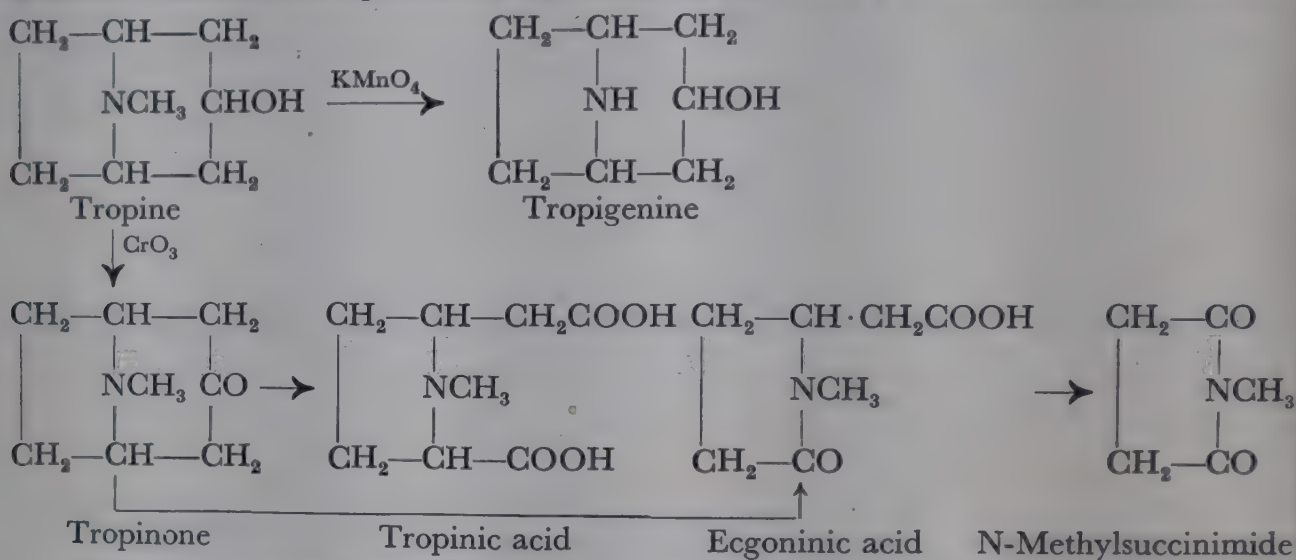
atropine	$\text{C}_{17}\text{H}_{23}\text{NO}_3$
hyoscyamine	$\text{C}_{17}\text{H}_{23}\text{NO}_3$
scopolamine	$\text{C}_{17}\text{H}_{21}\text{NO}_4$

Atropine. This alkaloid, isolated by Mein, and by Geiger and Hesse, in 1831, from the root of the deadly nightshade, is an ester. It decomposes on hydrolysis into *dl-tropic acid* (see p. 549) and the alkamine *tropine*:



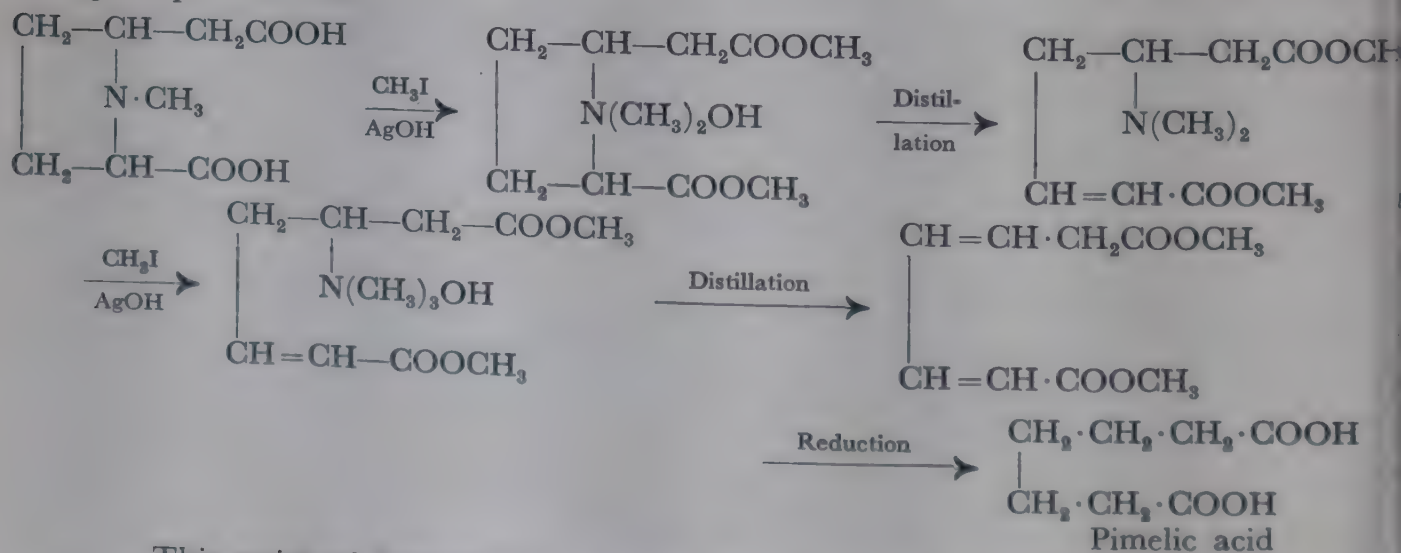
Ladenburg, Merling, and Willstätter, particularly, have investigated the constitution of tropine. The formula generally accepted to-day is that of Willstätter.

The oxidation of the base in alkaline solution with potassium permanganate eliminates the methyl group attached to nitrogen, and leads to *tropigenine*. In acid solution tropine is first oxidized by chromic acid to a ketone (*tropinone*), and this is further oxidized to *tropinic acid*, *ecgoninic acid*, and finally to N-methylsuccinimide:



The presence of a pyrrolidine nucleus in the tropine molecule is thus demonstrated.

The arrangement of the other carbon atoms is arrived at from the exhaustive methylation of tropinic acid, in which all the carbon atoms of tropine are still present. This leads to an unsaturated dicarboxylic acid, which, on reduction, gives pimelic acid:

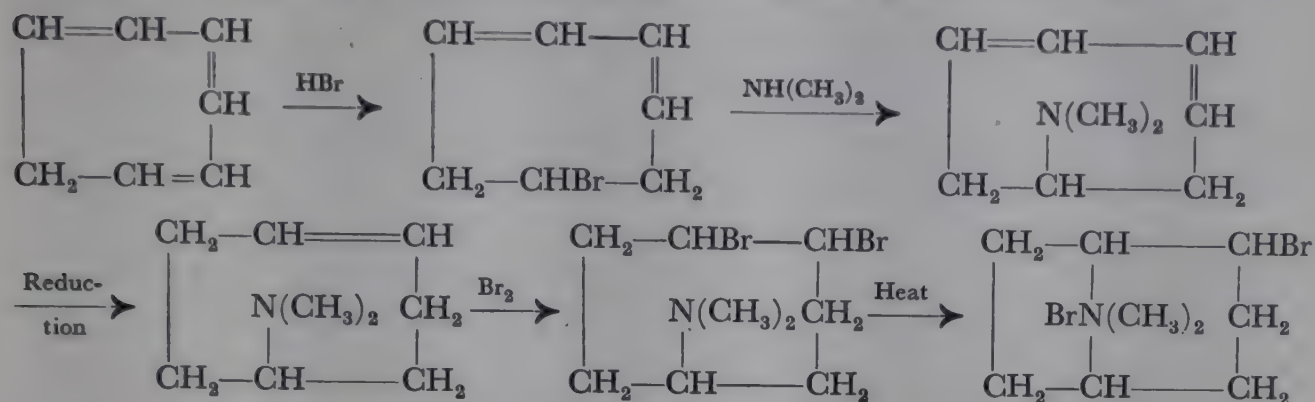


This series of degradations shows that tropine has an unbranched chain of seven carbon atoms. When other facts are taken into account, namely that the molecule contains a pyrrolidine ring, and that the keto-group of tropinone must lie between two CH_2 -groups (this is shown by the existence of a dibenzal- and

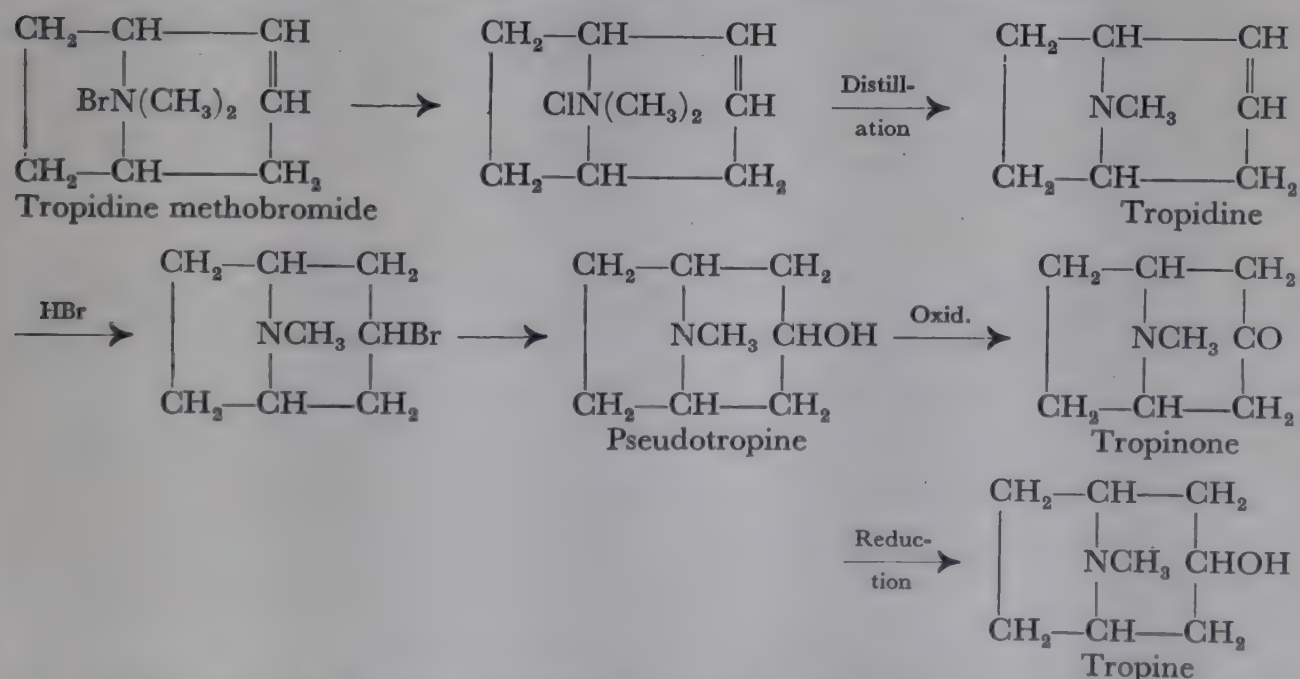
a di-isonitroso-compound), it follows most forcibly that tropine must have the foregoing formula.

This has been further confirmed by the degradation of tropine to *cycloheptatriene* (p. 743), and, in particular, by two syntheses of the alkaline.

The older synthesis (Willstätter) starts from the difficultly accessible *cycloheptatriene*, which is prepared from calcium suberate (p. 742). When treated with hydrobromic acid in the cold it is converted into bromocycloheptadiene. The bromine in this compound is then replaced by the $\text{—N(CH}_3)_2$ -group, and the dimethylamino-*cycloheptadiene* reduced to dimethylamino-*cycloheptene*. Bromine is then added on across the double bond, and the dibromo-addition product warmed, whereupon it isomerizes to bromotropane methobromide:



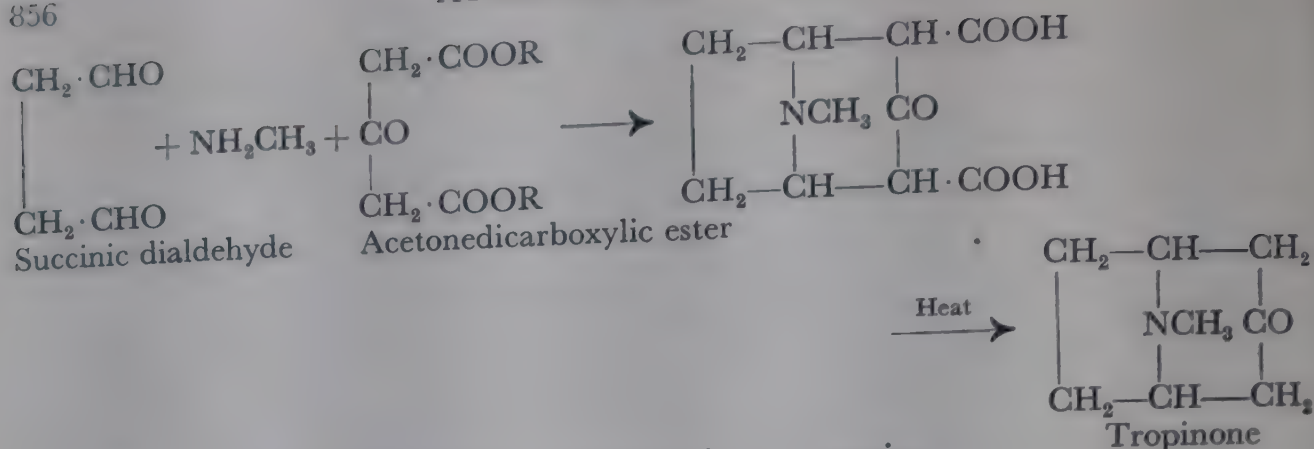
Treatment with caustic potash removes hydrogen bromide from the bromotropane methobromide. The bromide of the tropidine methobromide thus formed is replaced by chlorine, and the product distilled. The methochloride is thereby broken down into methyl chloride and tropidine. Addition of hydrogen bromide converts the latter into 3-bromotropane, and, by replacement of the bromine in this by the hydroxyl group, *pseudotropine*, a stereoisomeride of tropine, is formed. The conversion of this into tropine is carried out through the ketone (*tropinone*) which gives tropine on acid reduction (zinc and hydriodic acid):



A simpler and elegant synthesis of tropine has been discovered by R. Robinson. It depends on the condensation of succinic dialdehyde with acetonedicarboxylic ester and methylamine:

ATROPINE ALKALOIDS

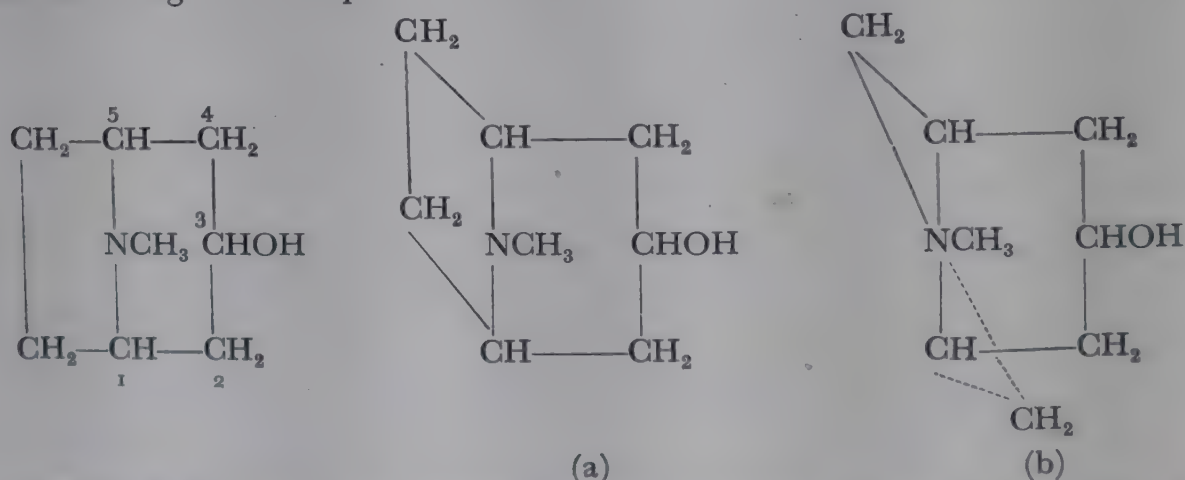
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The tropinone is reduced in acid solution to tropine.

C. Schöpf has shown that this and similar syntheses (e.g. those of pseudopelletierine and lobelanine) occur under physiological conditions, i.e. at ordinary temperatures and in a pH range not very far removed from neutrality. In the case of the above-mentioned synthesis of tropinone, even decarboxylation of the dicarboxylic acid first formed takes place smoothly at room temperature in an approximately neutral medium. The view that these alkaloids might be produced in the plant in a similar way thus receives support.

In the tropine molecule there are two structurally equivalent asymmetric carbon atoms (1 and 5), which occupy the points at which the nitrogen bridge is attached, and which belong in common to the pyrrolidine and piperidine rings. There should therefore exist a *cis*-form (internally compensated) (a), and a racemic *trans*-form (b). The latter would not, however, appear to be capable of existence. The carbon bridge $-\text{CH}_2 \cdot \text{CH}_2-$ which links the asymmetric carbon atoms, is attached in the *cis*-position (a) and not the *trans*-position (b) to the piperidine ring of the tropine molecule.



There is thus only one tropane (parent substance of tropine; contains a H-atom instead of the OH-group), and one tropinone, which are both optically inactive. *Tropine* (m.p. 63°, b.p. 233°) has, on the other hand, a stereoisomeride in *pseudotropine* (m.p. 108°, b.p. 240–241°). In the internally compensated tropine the asymmetric carbon atoms 1 and 5 possess inherently opposite configurations. The carbon atom 3 which carries the hydroxyl group thus becomes pseudo-asymmetric. Hydroxyl and hydrogen can exchange places, giving rise to the existence of two isomerides, which actually exist as tropine and pseudotropine. Both have a symmetrical structure, and thus have no effect on polarized light.

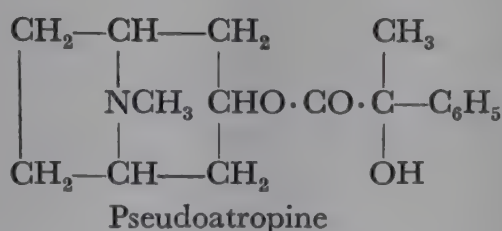
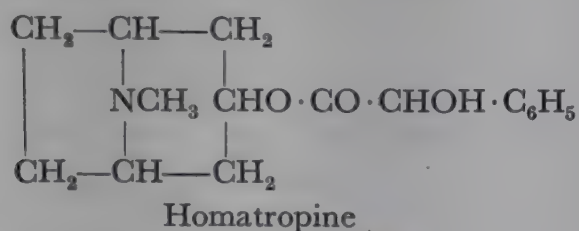
By the esterification of *dl*-tropic acid with tropine, best by combining acetyl-tropyl chloride with tropine, and subsequently removing the acetyl radical, *atropine* is obtained synthetically. The total synthesis of atropine has thus been accomplished.

PHYSIOLOGICAL ACTION OF ATROPINE. Atropine dilates the pupil of the eye, i.e. it has a mydriatic action. It is therefore widely used in ophthalmic surgery. It also paralyses all the nerve endings that muscarine stimulates, and is therefore an antidote for fly agaric poisoning. Even in small doses it inhibits glandular secretion, and diminishes or prevents the flow of saliva and the formation of perspiration and mucus, and is used for these purposes in medicine.

Tropeines. Under this heading, Ladenburg classed the esters of tropine with acids in general; they differ from atropine in the nature of the acid radical. The alkaloids hyoscyamine (see p. 858), and atropine (see p. 853) can be regarded as particular tropeines. Such types are found also in *Duboisia myoporoides*, viz. *poroidine* (the isovaleric acid ester of nortropine) and *isoporoidine* (the 2-methylbutyric acid ester of nortropine).

The characteristic physiological action of atropine and its importance in medicine have given rise to the preparation of new substances with different acid and alkamine components in attempts to make substances with similar or different activity. The group of tropeines and analogous esters has therefore been very thoroughly studied.

BENZOYLTROPEINE, $C_8H_{14}NO \cdot COC_6H_5$, CINNAMYLTROPEINE, $C_8H_{14}NO \cdot COCH=CHC_6H_5$, and SALICYLTROPEINE, $C_8H_{14}NO \cdot COC_6H_4OH$, which are obtained from tropine and the acid concerned, do not possess mydriatic properties. On the other hand, the *mandelic ester of tropine* (*homatropine*) and *atrolactyltropine* (*pseudoatropine*) enlarge the pupils:

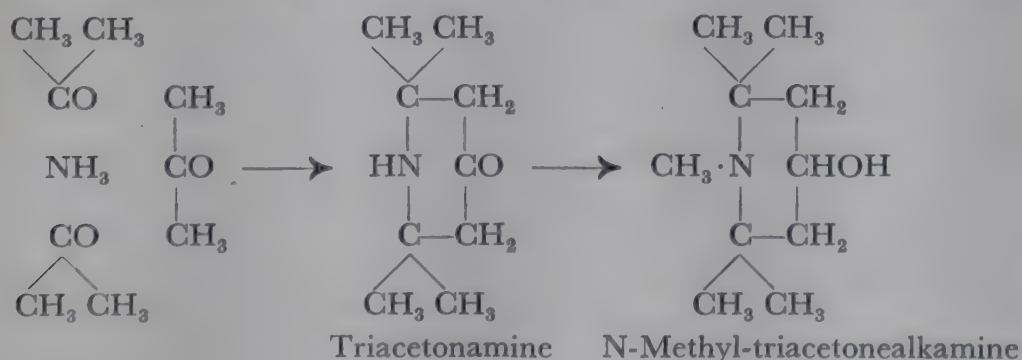


The existence of mydriatic action seems to depend upon the combination of tropine with an aromatic-aliphatic carboxylic acid which contains a hydroxyl group in the aliphatic part. This can, however, in certain instances be replaced by chlorine, since β -chloro-hydratropyl-tropine,



and the analogous bromine compound also enlarge the pupils.

Attempts to use simpler alkamines for esterification instead of tropine have met with considerable success. Thus acetone and ammonia give, fairly readily, "*triacetoneamine*", or α, α' -tetramethyl- γ -piperidone (Heintz), which on reduction and subsequent methylation is converted into N-methyl-triacetonealkamine:



The mandelic ester of N-methyl-triacetonealkamine has a mydriatic action, like *euphthalmine*, which differs constitutionally from the former only in having one C-methyl group less.

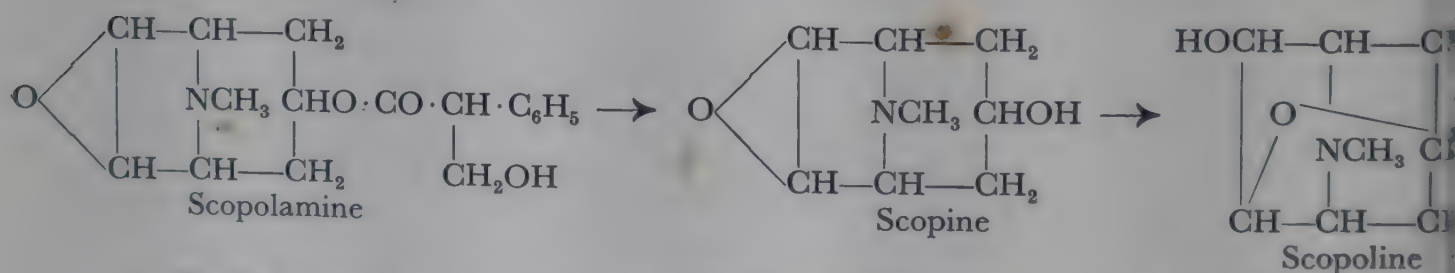
Hyoscyamine, discovered by Geiger and Hesse in 1833 and present in *Solanaceæ* in considerable quantities, is very similar to atropine in all its properties. It differs from it in constitution only in that it contains optically active tropic acid as its acid component, whereas atropine contains the racemic form of the acid. Hyoscyamine is the *l*-tropic ester of tropine. It can be hydrolysed by hot water to tropine and lævorotatory tropic acid, and can be resynthesized from these fission products. It melts at 108.5° ; $[\alpha]_{\text{D}}^{22} = -20.7^{\circ}$.

Convolamine. Orechoff discovered an alkaloid in *Convolvulus pseudocantabricus* which, on alkaline hydrolysis, broke down into tropine and veratric acid. It is therefore veratroyltropine. It melts at $114-115^{\circ}$. The plant also contains the base *convolvine*, which has been recognized as veratroylnortropine.

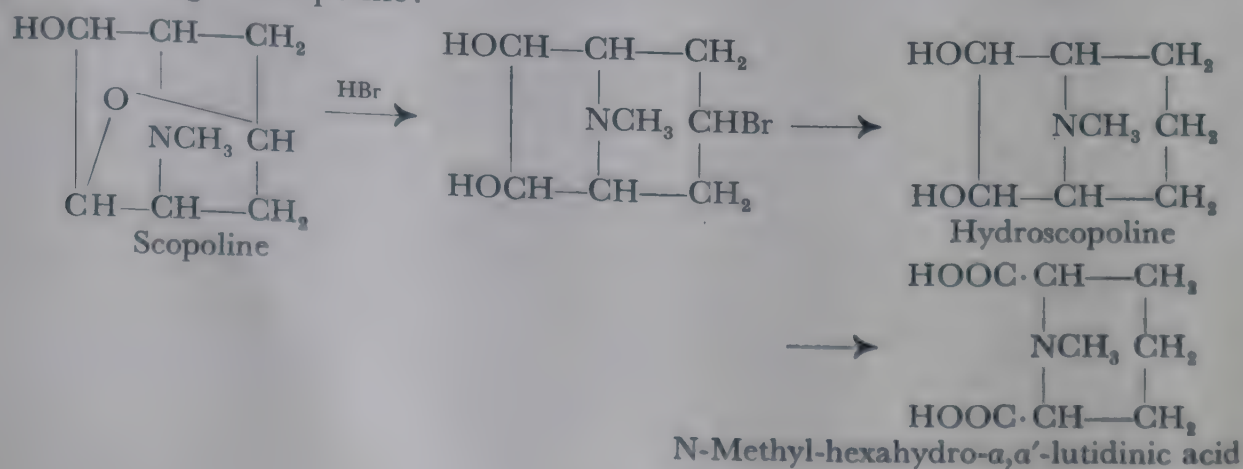
Scopolamine (Hyoscine), $\text{C}_{17}\text{H}_{21}\text{NO}_4$. This important alkaloid is fairly widely distributed in *Solanaceæ*. It was discovered by E. Schmidt in 1888 in species of *Scopolia*. *dl*-Norscopolamine (*dl*-norhyoscine) has been isolated from the mother liquors of the manufacture of scopolamine.

Alkaline or acid hydrolysis converts scopolamine into *tropic acid* and *scopoline* (*oscine*), $\text{C}_8\text{H}_{13}\text{NO}_2$. It is, therefore, related to atropine, and differs from it in the nature of the alkamine component.

Scopoline, however, is not contained as such in scopolamine, but is the product of a rearrangement. If scopolamine is hydrolysed in the most gentle way possible, e.g. enzymatically (lipase) or with ammonia and ammonium chloride, the primary fission product is *scopine*, which very readily passes into scopoline. According to Gadamer, Hess, and Willstätter, the formulæ of these bases may be represented as follows:



Hydrobromic acid breaks the oxygen bridge of scopoline and produces hydroscopoline bromide. The bromine of this may be removed by reduction with zinc and sulphuric acid, hydroscopoline being formed. This can be oxidized to N-methyl-hexahydro- α, α' -lutidinic acid, thus confirming the existence of the piperidine ring in scopoline:



Scopolamine melts at 59° (monohydrate), $[\alpha]_D = -33^{\circ}$. Like atropine it possesses mydriatic properties, and exerts a paralyzing action on the nervous system. Its action differs from that of atropine in that no excitatory condition precedes the depressory stage. For this reason scopolamine is used as a sedative, and in combination with morphine for the production of "twilight sleep" and narcosis.

2. Cocaine group

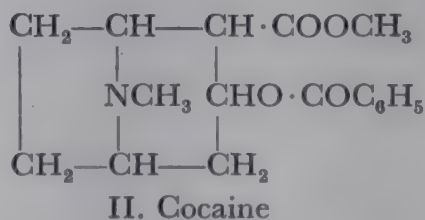
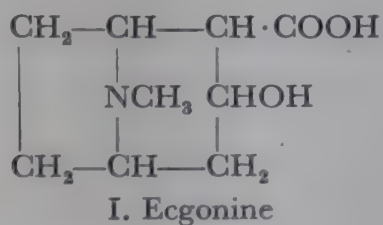
The leaves of the shrub *Erythroxylon coca* contain a series of closely related alkaloids, including cocaine, cinnamylcocaine, benzoylecgonine, α - and β -truxilines, and tropacocaine. In addition, the South American coca leaves also contain hygrine and cuscohygrine, which have already been dealt with as pyrrolidine alkaloids. A dihydroxytropene has recently been isolated from the mother liquor from the preparation of coca alkaloids after hydrolysis.

Cocaine, $C_{17}H_{21}NO_4$. This important alkaloid was isolated by Niemann in 1860 from coca leaves. The South American leaves contain a relatively large quantity of cocaine (up to about 1.3%) and little in the way of subsidiary bases. In the Javanese leaves the subsidiary alkaloids predominate (about 75% of the total bases).

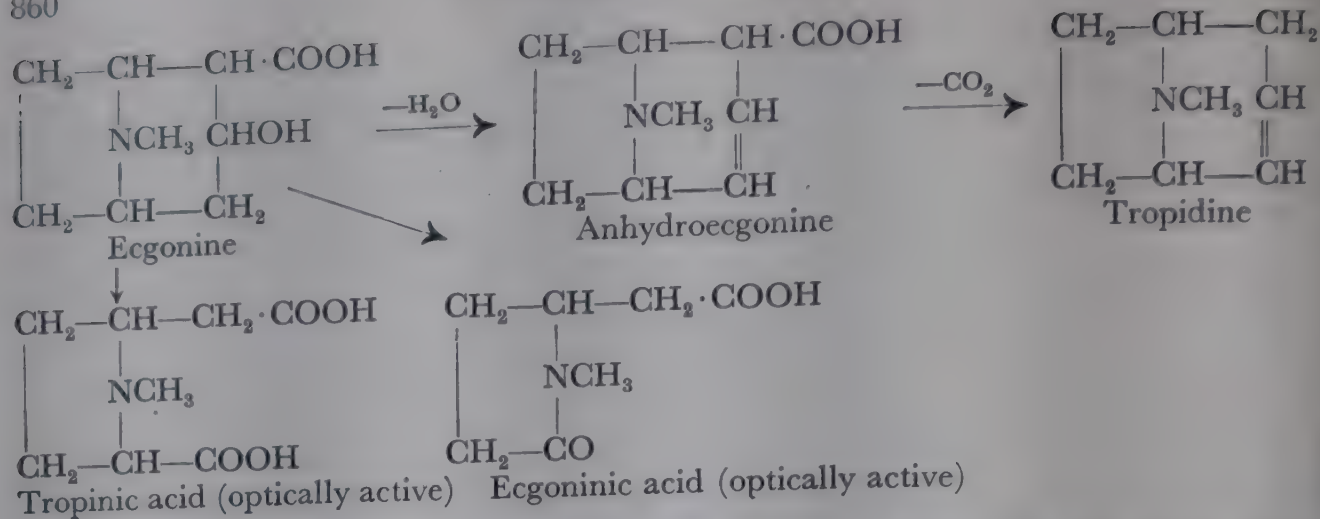
The elucidation of the constitution of cocaine is closely connected with that of tropine, as the two bases are intimately related.

On hydrolysis with acids or alkalis cocaine gives benzoic acid, methyl alcohol, and a fission product $C_9H_{15}NO_3$, *ecgonine*. This contains a carboxyl group, an alcoholic hydroxyl group, and has the character of a tertiary amine. Oxidative studies throw light on its constitution. Chromic acid oxidizes ecgonine first to tropinone (see p. 860), and then further to tropinic and ecgoninic acids (see p. 860). From the formation of tropinone it follows that the hydroxyl group of ecgonine must occupy the same position as in tropine (carbon atom 3). The production of tropinic and ecgoninic acids as decomposition products of ecgonine shows that the carboxyl group is in the piperidine and not in the pyrrolidine half of the molecule, since if this were not so a carboxylated tropinic acid would be expected to be formed.

On the basis of these degradation reactions the formula of ecgonine is found to be I, and that of cocaine II:

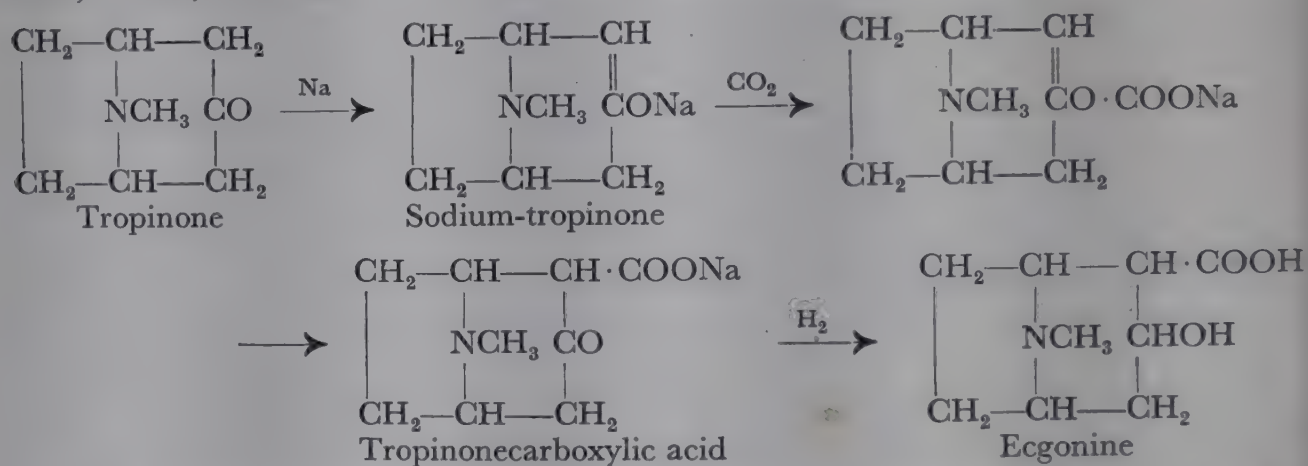


The elimination of water from ecgonine converts it into *anhydroecgonine*. The latter is decomposed by heating with hydrochloric acid to 280° into carbon dioxide and *tropidine*. The following formulæ illustrate these reactions as well as the oxidation of ecgonine to tropinic and ecgoninic acids:

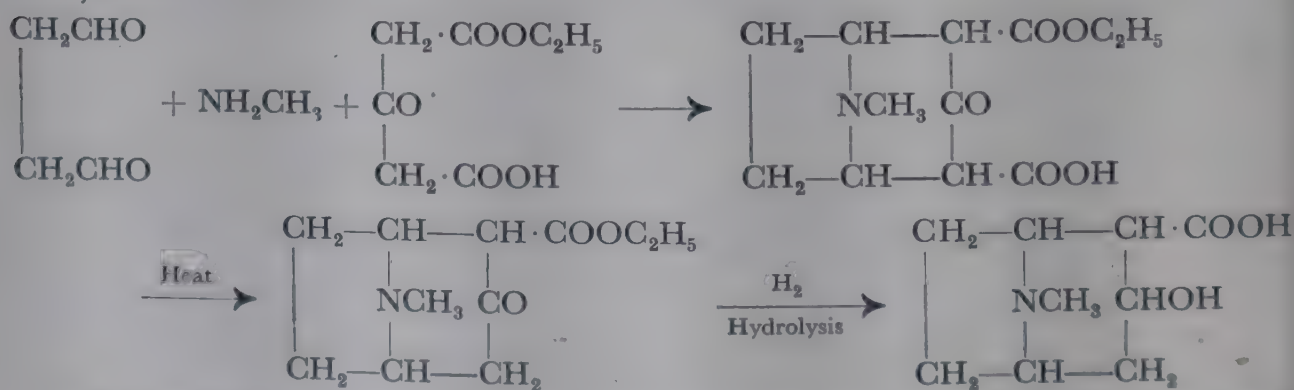


Whilst tropinic and ecgoninic acids from tropine have, like the latter base, no action on polarized light, the two acids are obtained in the active forms from optically active ecgonine, the tropinic acid being dextrorotatory and the ecgoninic acid lævorotatory.

The constitution of ecgonine has been confirmed by two syntheses of the compound (Willstätter). One of these makes use of the addition of carbon dioxide to the sodium compound of tropinone. This gives rise to tropinonecarboxylic acid, which, on reduction is converted into ecgonine:



The second synthesis is based on that of tropinone by Robinson and depends on the condensation of succinic dialdehyde, acetonedicarboxylic acid mono-ethyl ester, and methylamine:



Ecgonine has four asymmetric carbon atoms, and should therefore be able to exist in 16 stereoisomeric forms. Since, however, the $-\text{CH}_2\cdot\text{CH}_2-$ bridge which is attached to the piperidine ring of ecgonine, can only be arranged in the *cis*-position, as in the case of tropine (see p. 856), the number of presumably stable isomerides of ecgonine is reduced to half this number, viz. 8. Several of these and of the corresponding cocaines are known.

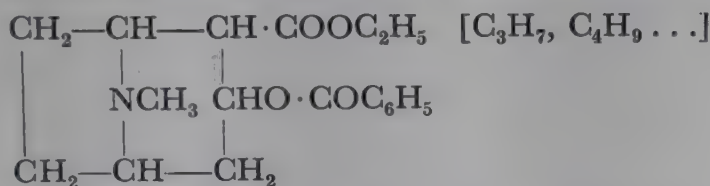
In coca leaves ordinary *l*-cocaine is found (m.p. 98° , $[\alpha]_D = -15.8^{\circ}$) and, in smaller amounts, *d*-pseudococaine (m.p. $46-47^{\circ}$). The latter is derived from the *d*-ecgonine (*d*-pseudoecgonine), which, according to Einhorn, is obtained on warming *l*-ecgonine with caustic potash.

In most cases, industrially, the total, crude coca-alkaloids are hydrolysed to ecgonine, and the latter then reconverted to cocaine by simple methods (esterification with methyl alcohol, and benzoylation).

PHYSIOLOGICAL ACTION. Cocaine paralyses the peripheral nerves, and is therefore a powerful anæsthetic, and is much used. It causes dilatation of the pupil of the eye, which is not complete, and can be suppressed by pilocarpine and physostigmine. After resorption cocaine acts on the central nervous system (dizziness, stimulation, paralysis). Death is due to paralysis of the respiratory centre. Repeated doses of cocaine soon produce acclimatization.

Cocaine increases the temperature of the animal body considerably. Next to tetrahydro- β -naphthylamine it is the strongest fever-producing substance.

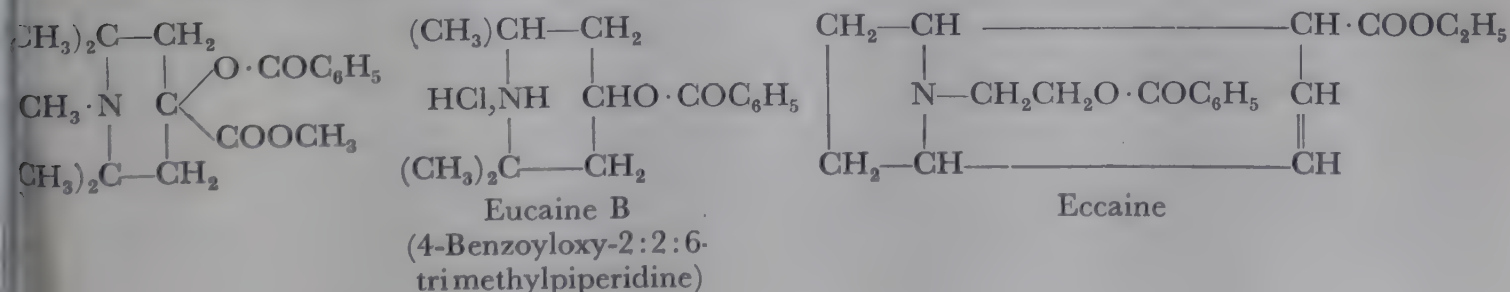
SUBSTANCES RELATED TO COCAINE. By making diverse modifications in the cocaine structure, an attempt has been made to obtain an insight into the relationships which exist between chemical constitution and anæsthetic action in such types of compound. Ecgonine has no anæsthetic power; nor have benzoylecgonine or ecgonine methyl ester. It therefore appears to be necessary for both the free hydroxyl and free carboxyl in ecgonine to be blocked in order to produce anæsthetic properties. The nature of the alcoholic component then appears to be in no way critical. Benzoylecgonine ethyl ester (*cocæthyline*) and the analogous propyl, butyl, etc. esters proved also to be powerful anæsthetics.



The influence of the acid radical which esterifies the alcoholic hydroxyl group in the ecgonine molecule is more pronounced. Only a few acids are suitable. Whilst chloro- and nitrococaines (prepared by using chloro- or nitrobenzoic acids, respectively) as well as *m*-amino- and *m*-hydroxycocaines have practically no anæsthetic action, the carbonic esters of aminococaines are powerful anæsthetics.

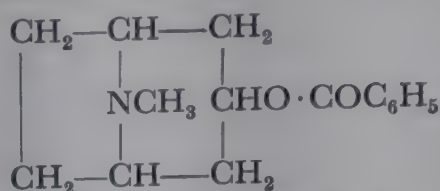
Numerous useful substitutes for cocaine have recently been prepared. Thus, starting from triacetoneamine (see p. 857), O-benzoyl-N-methyl-triacetone-alkamine-carboxylic acid methyl ester has been obtained; its hydrochloride has been introduced into medicine under the name of *eucaïne A* (Merling). It is a fairly powerful anæsthetic, and is less toxic than cocaine. It has no action on the pupil of the eye.

Eucaïne B and eccaine are similar in action:



The benzoic and *p*-aminobenzoic esters of many simple aliphatic amino-alcohols also display anæsthetic properties and are largely used. See novocaine, panthesine, tutocaine, etc. (p. 248).

Tropacocaine, $C_{15}H_{19}NO_2$. Tropacocaine occurs in the cocaine alkaloids of Javanese coca leaves, but it belongs constitutionally to the atropine group, as it is the *benzoic ester of pseudotropine* (see p. 856):

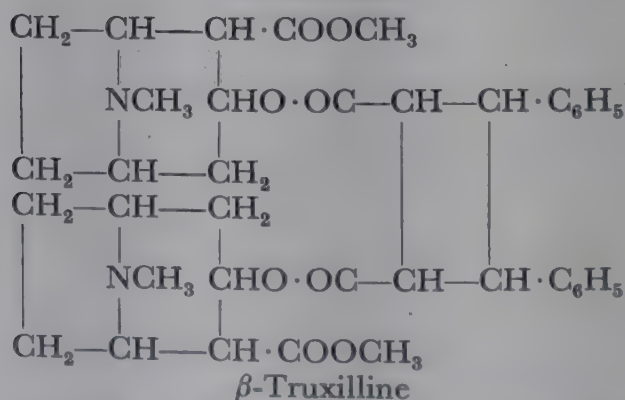
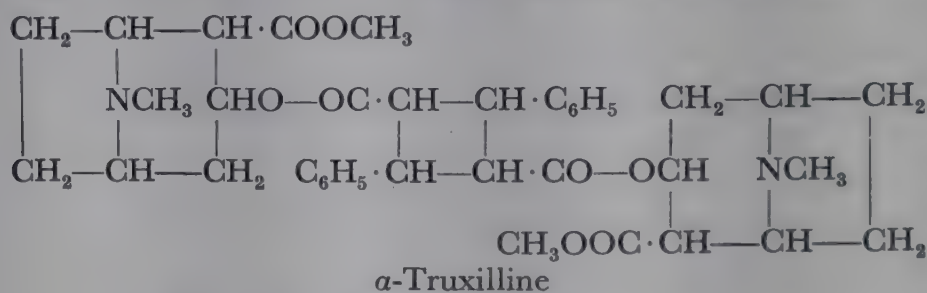


It melts at 49° . The alkaloid, which is also obtainable synthetically by benzoylation of pseudotropine, has a powerful anæsthetic action, though the stereoisomeric benzoyltropeine is not lacking in this respect.

Cinnamylcocaine, $C_{10}H_{23}NO_4$. As cinnamylcocaine is hydrolysed to cinnamic acid, methyl alcohol, and ecgonine, it is recognized as cinnamylecgonine methyl ester (Liebermann). It can be resynthesized from these fission products. It melts at 121° .

The amount of cinnamylcocaine in Javanese coca leaves is considerable.

α - and β -Truxilline, $C_{38}H_{46}N_2O_8$. These two bases, which were first secured from coca leaves in a state of purity by Liebermann, also belong to the group of acylecgonine methyl esters, the OH-group of ecgonine having reacted with α -truxillic acid and β -iso-truxillic acid respectively (see p. 651-2). Their formulæ are therefore:



α -Truxilline is amorphous and melts at 80° . It is laevorotatory. β -Truxilline sinters at 45° , $[\alpha]_D = -29.3^\circ$. Neither α - nor β -truxilline has anæsthetic powers.

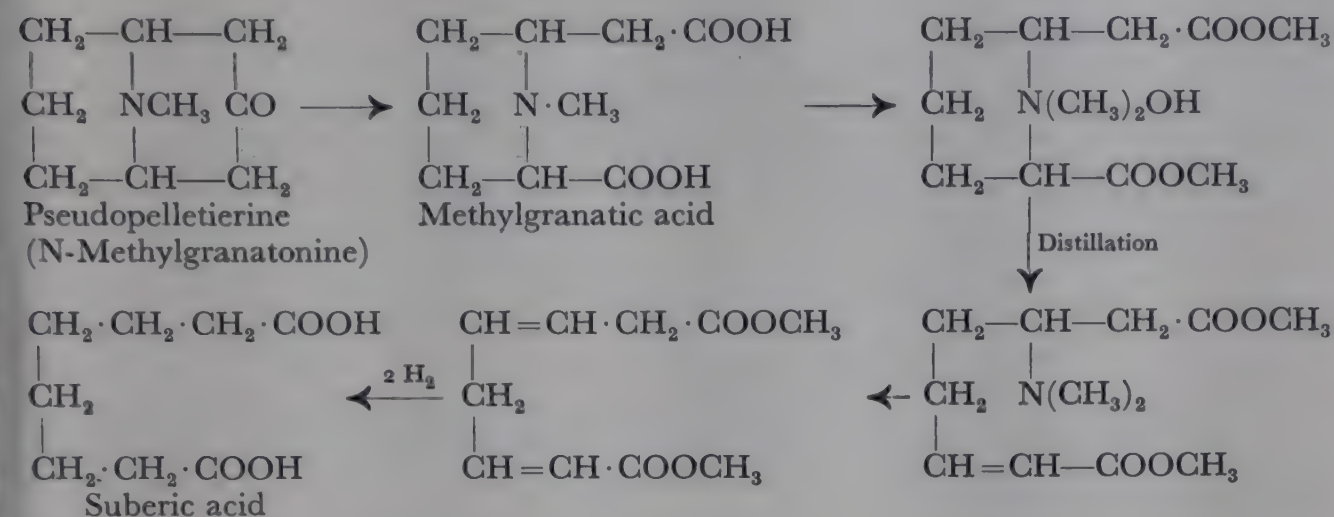
Benzoylecgonine, $C_{16}H_{19}NO_4$, occurs in very small quantities in coca leaves but it can easily be synthesized from ecgonine and benzoic anhydride. The melting point of the anhydrous substance is 195° . It is distinguished from all other coca-alkaloids by its acidic character, to which indeed it owes its slight toxicity. It is about twenty times less poisonous than cocaine.

3. Alkaloids of pomegranate bark

In the bark of *Punica granatum* L. there is a series of different alkaloids, of which four were described by Tanret in 1877: *pseudopelletierine*, *pelletierine*, *isopelletierine*, and *methylpelletierine*.

Pseudopelletierine (N-Methylgranatonine), $C_9H_{15}NO$. The work of Ciamician and Silber, which was followed up by Piccinini and Willstätter shows that N-methylgranatonine is the higher ring homologue of tropinone and contains two condensed piperidine rings.

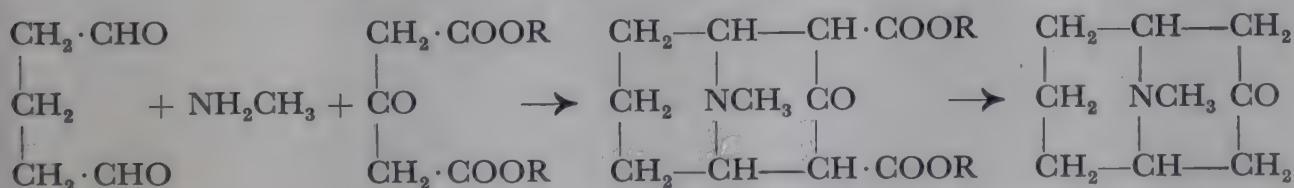
By oxidation it is converted into methylgranatic acid which on exhaustive methylation furnishes an unsaturated dicarboxylic acid, which can be reduced to suberic acid:



Like tropinone, N-methylgranatonine combines with benzaldehyde to give a dibenzal-compound. Distillation with zinc dust gives α -propylpyridine. By reduction, two stereoisomeric *N-methylgranatolines* are produced (according to the experimental conditions), which correspond to tropine and pseudotropine, and differ in the arrangement of the hydroxyl group in space.

The elimination of nitrogen from the pseudopelletierine molecule *without opening the cyclooctane ring which is present in the alkaloid* is possible by exhaustive methylation. In this connection, see the degradation reactions of pseudopelletierine to *cyclooctatriene* and *cyclooctatetraene* (p. 747).

Finally, Robinson has synthesized N-methylgranatonine by a simple method, based on his synthesis of tropinone. Condensation of glutardialdehyde with acetonedicarboxylic ester and methylamine gives the ester of a dicarboxylic acid; the free dicarboxylic acid decomposes to carbon dioxide and pseudopelletierine:



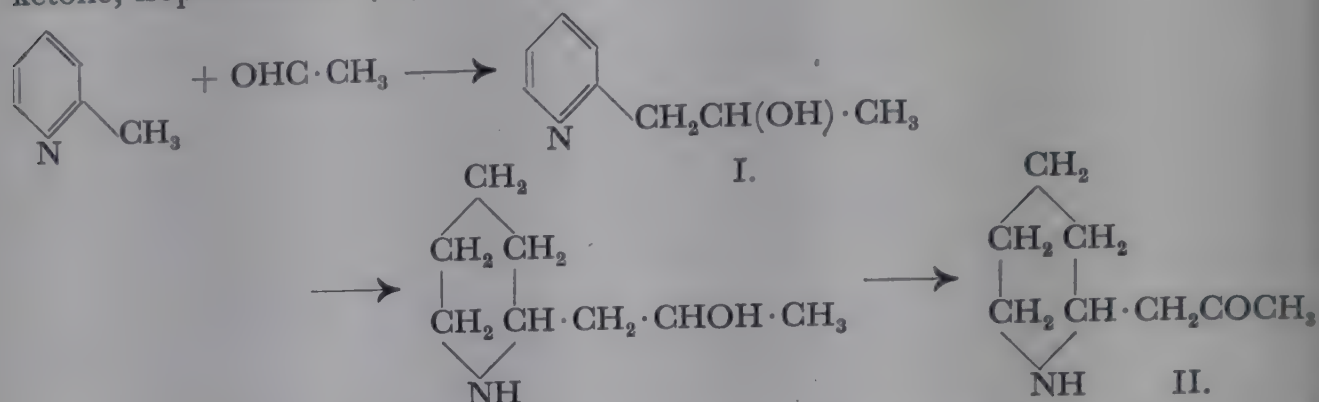
Pseudopelletierine melts at 48° and boils at 246° . It is optically inactive.

PHYSIOLOGICAL ACTION. The bark of the pomegranate tree has been used for a long time as an anthelmintic. It appears to owe this property particularly to pelletierine (and isopelletierine?). The alkaloids are fairly toxic to warm-blooded animals.

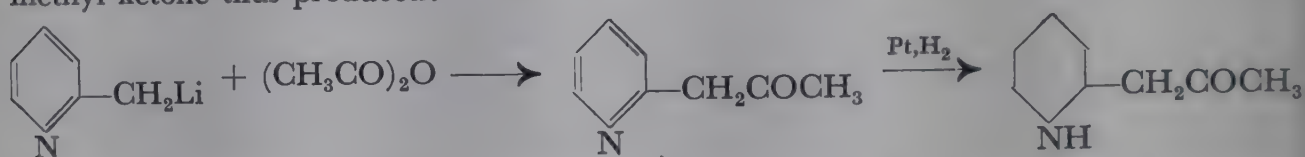
The most diverse compounds act as anthelmintics. Thus, the alkaloids *surinamine* and *arecoline*, as well as the non-alkaloids *filicic acid*, *filmarone* (phloroglucinol derivatives from the fern), and *santonin* (naphthalene derivative) are amongst those which possess this power.

The anthelmintic properties of pumpkin seeds, garlic, worm-moss, etc., are well known.

Isopelletierine. This base is ketonic in nature, and is closely related to conhydrine (see p. 848). Its synthesis was carried out by Meisenheimer, and begins with the condensation of α -picoline with acetaldehyde to picolyl-methyl-carbinol (I), which is subsequently reduced in its pyridine half, and then oxidized to the ketone, isopelletierine (II):



According to a more recent synthesis by Wibaut, isopelletierine may also be obtained by the action of acetic anhydride on lithium-picolyl, followed by reduction of the picolyl methyl ketone thus produced:



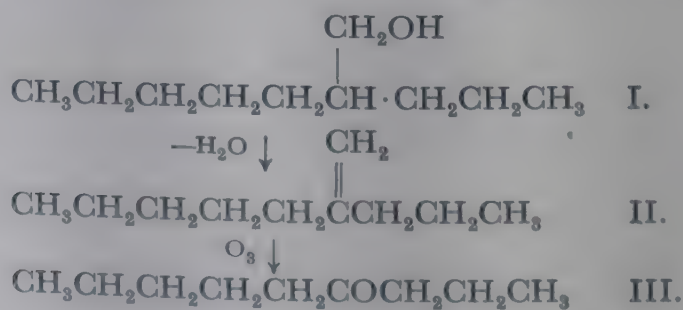
Methylisopelletierine is isopelletierine methylated at the nitrogen atom.

4. Alkaloids of the Broom and Lupin group

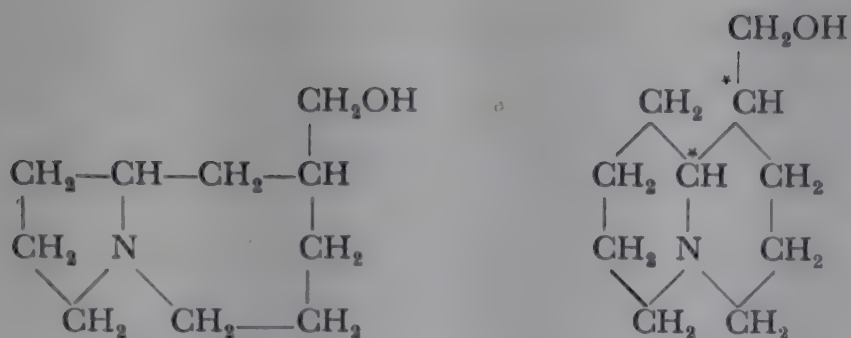
The alkaloid *sparteine* occurs very abundantly in broom (*Spartium scoparium* L.). The same base is also found in the seeds of the yellow lupin, which contain in addition the alkaloid *lupinine*, $\text{C}_{10}\text{H}_{19}\text{NO}$, (and secondary alkaloids).

Lupinine, $\text{C}_{10}\text{H}_{19}\text{NO}$, a beautifully crystalline alkaloid, melting at 69° , contains a nitrogen atom which belongs to two rings, and also a primary alcohol group, since it can be oxidized to a carboxylic acid, *lupininic acid*, which contains the same number of carbon atoms as the base itself.

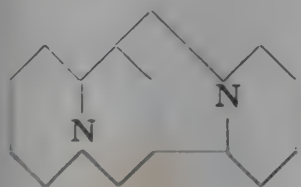
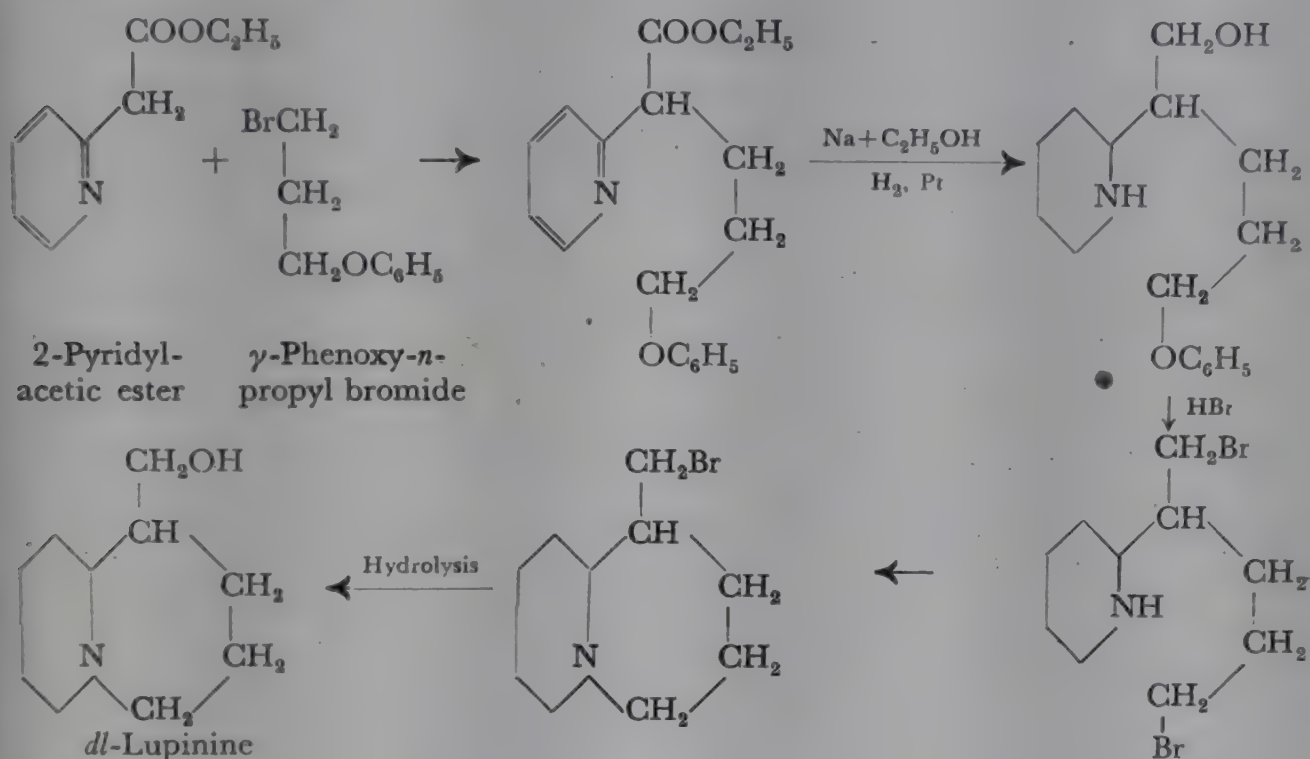
Exhaustive methylation of lupine, together with reduction of the unsaturated intermediate products leads to the saturated alcohol (I), whose constitution is determined by its decomposition to *n*-amyl *n*-propyl ketone (III):



It follows that lupinine must have one of the two following formulae. The second is the more probable (Karrer):



The correctness of the second of these has been established by the synthesis of lupinine derivatives and of racemic lupinine itself. In the first place, Winterfeld has prepared " β -lupinane" (derived from lupinine by replacement of OH by H) synthetically by a straightforward reaction and finally G. R. Clemo has obtained racemic lupinine itself as follows:



Sparteine, $C_{15}H_{26}N_2$. The accompanying constitutional formula has been proposed for this base, which indicates its close relationship to lupinine. It is an oil, boiling at 326° (754 mm), $[\alpha]_D = -16.4^\circ$.

CHAPTER 68. CINCHONA ALKALOIDS

(ALKALOIDS WITH A QUINOLINE RING)

In the trunk, branch, and root barks of various trees of the species *Cinchona* and *Remijia* (cinchona tree), very many different alkaloids are found (more than 25), of which the most important are *cinchonine* and *quinine*. Since the XVIIth century "cinchona bark" has been used in Europe as a febrifuge. It is particularly valuable in cases of malaria. The home of the "fever tree" is South America.

From there it was taken to India and Java, where it is now specially cultivated. Most of the cinchona bark imported into Europe comes from this source.

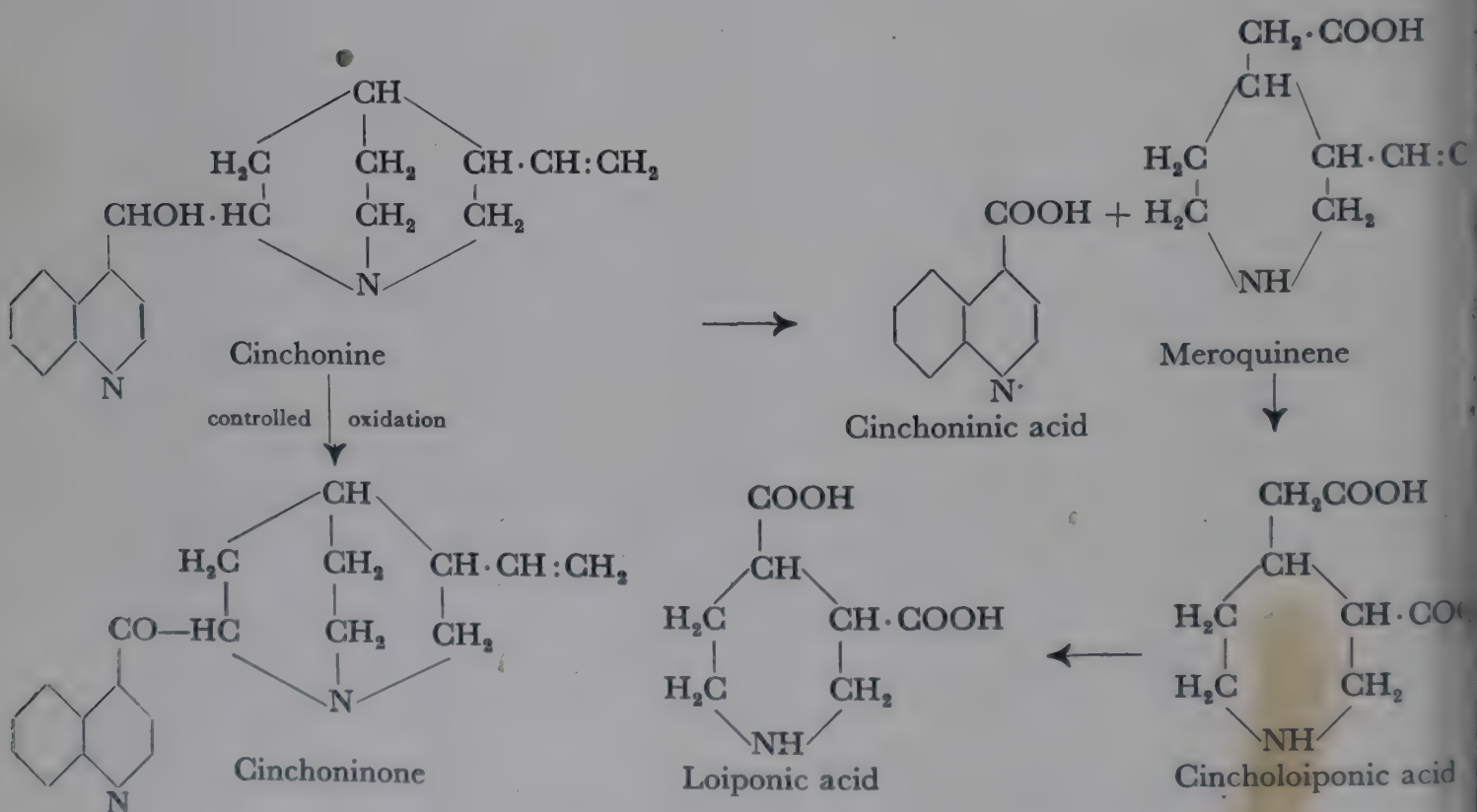
(The name "cinchona" was given to this family of plants by Linné (1742) because in 1638 the Vicereine of Peru, Cinchon, had been cured of fever by the use of the bark of these trees).

Only the most important of the cinchona alkaloids whose structures have been elucidated can be dealt with here. These are *cinchonine*, *cinchonidine*, *cupreine*, *quinine*, *quinidine*, *hydrocinchonine*, *hydroquinine*, and *hydroquinidine*.

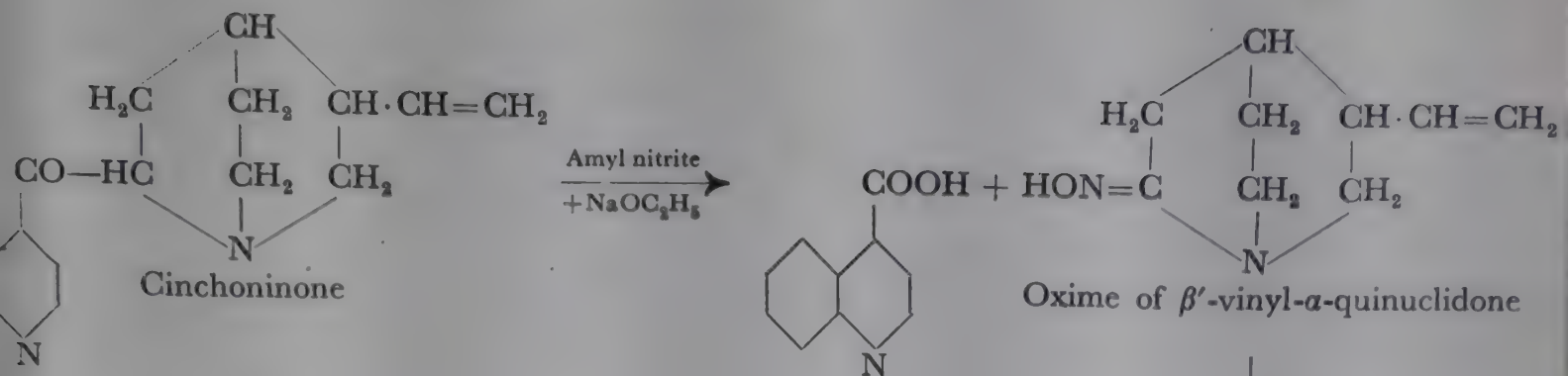
Cinchonine, $C_{19}H_{22}N_2O$. Pelletier and Caventou discovered this alkaloid in cinchona bark in 1820.

Of the two nitrogen atoms one is tertiary, and belongs to two ring systems. The other occurs in a quinoline ring. The oxygen is present as a secondary alcohol group, since the alkaloid may be converted by controlled oxidation into a ketone (*cinchoninone*).

Cinchonine is oxidized by chromic acid to two characteristic fission products — *cinchoninic acid* and *meroquinene*. The latter partially undergoes further oxidation, being converted into *cincholoiponic acid* and finally into *loiponic acid* (Skraup and Königs):

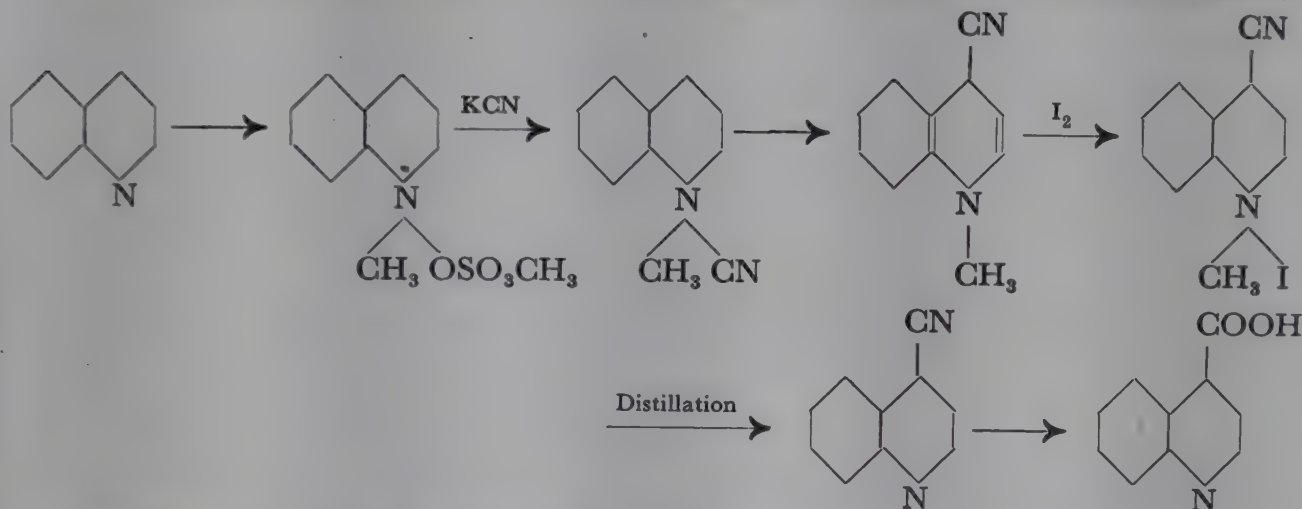


The bicyclic, hydrogenated half of the cinchonine molecule is called the "*quinuclidine residue*". It can be obtained in the form of an *isonitroso-derivative* by acting upon cinchoninone with nitrous acid. This smooth fission of cinchonine (Rabe) gives cinchoninic acid in almost 90% yield, and α -oximino- β' -vinyl-quinuclidine in about 75% overall yield:

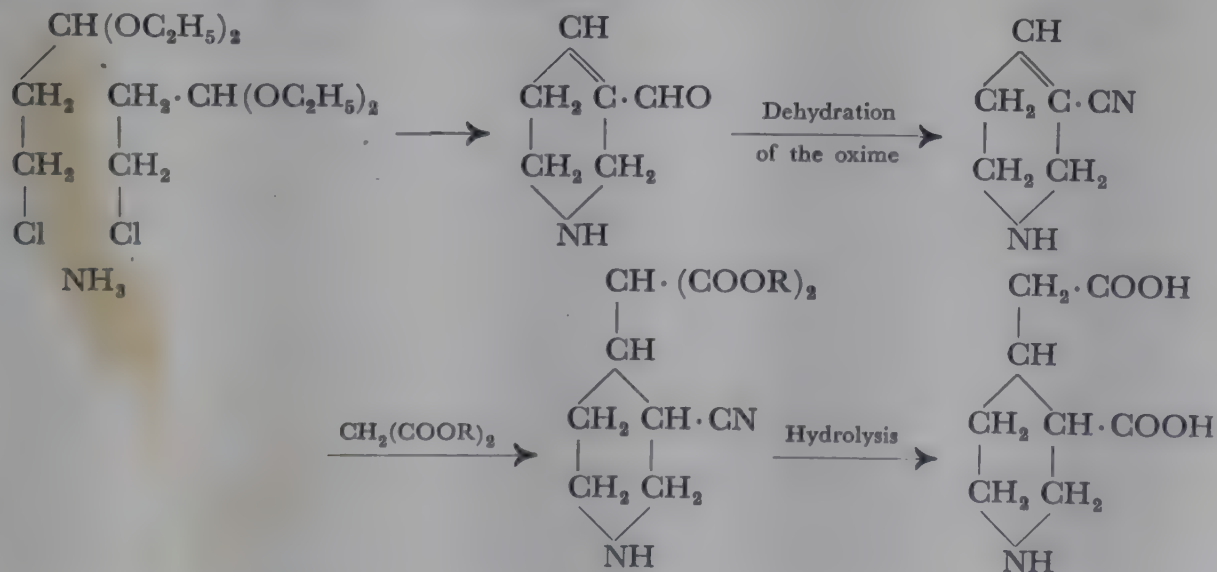


The constitutions of the fission products of cinchonine have been completely elucidated, and they have been prepared synthetically.

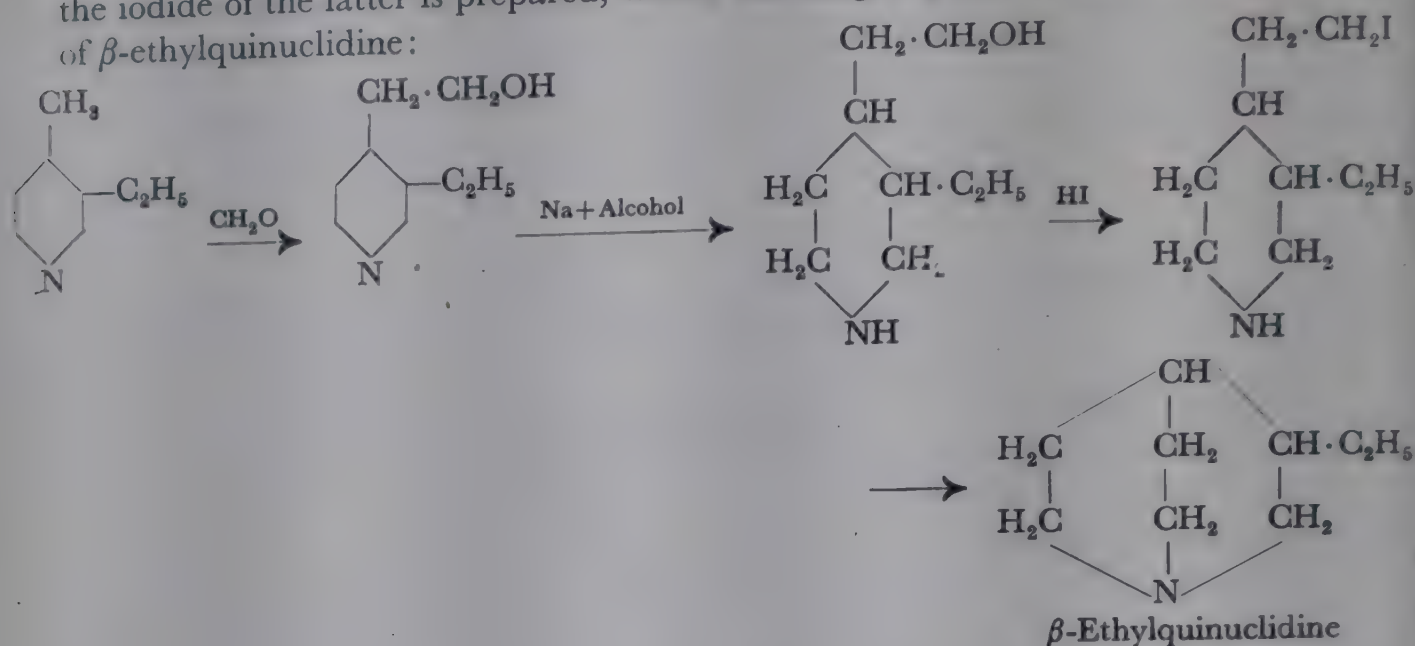
Cinchoninic acid is best prepared from quinoline. The methosulphate, obtained by the addition of dimethyl sulphate, is treated with potassium cyanide, whereby 1-methyl-4-cyano-1:4-dihydroquinoline is produced. With iodine, this is converted into 4-cyanoquinoline methiodide, which affords 4-cyanoquinoline on distillation; hydrolysis of this nitrile finally gives cinchoninic acid (Kaufmann):



Wohl synthesized cincholoiponic acid by condensing β -chloropropionacetal with ammonia to Δ^{β} -tetrahydropyridine- β -aldehyde, converting this into Δ^{β} -tetrahydropyridine- β -nitrile, adding malonic ester to the latter, and hydrolysing, when the desired acid was obtained:

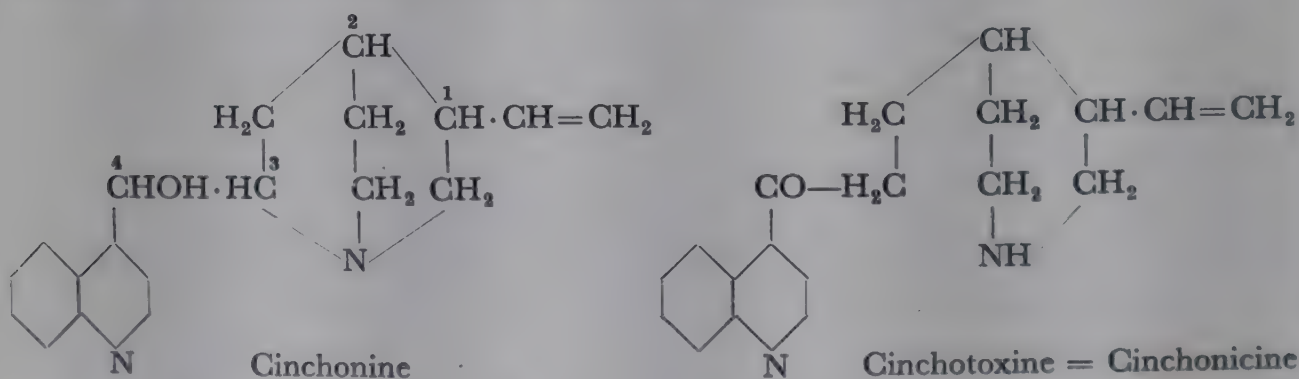


Finally, β -ethylquinuclidine can also be prepared synthetically (Königs). γ -Methyl- β -ethylpyridine (β -collidine) is condensed with formaldehyde to methylol- β -collidine. After reduction of this compound to the hexahydro-base, the iodide of the latter is prepared, which rearranges spontaneously to the iodide of β -ethylquinuclidine:



The constitution of cinchonine would thus appear to have been elucidated fully on all scores, on the basis of the highly successful degradation reactions and the straightforward syntheses of the fission products.

The alkaloid undergoes a remarkable rearrangement when it is warmed for some time with acetic acid or phosphoric acid. The reaction product is a ketone (*cinchotoxine* or *cinchonicine*) produced by the so-called "hydramine fission", which has often been observed to take place with alkamines bearing hydroxyl and nitrogen on neighbouring carbon atoms (cf. ephedrine, p. 839):



Cinchonine melts at 264° ; $[\alpha]_D^{17} = +223^{\circ}$. It is only very slightly soluble in water and alkalis, but dissolves easily in acids, alcohol, and chloroform.

Cinchonidine, $C_{19}H_{22}N_2O$. This base, isomeric with cinchonine, gives the same fission products as this substance, and must therefore be stereoisomeric with it.

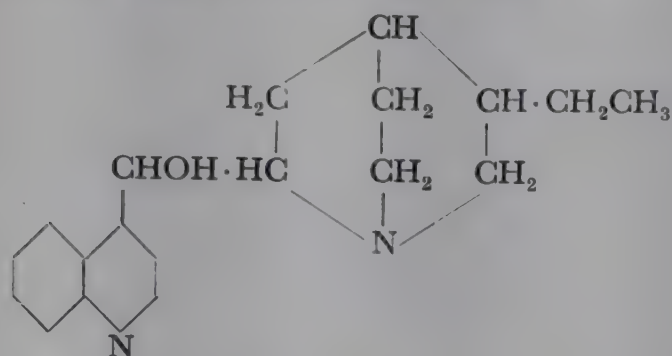
The four asymmetric carbon atoms of cinchonine (1,2,3,4; see formula above) make possible the existence of sixteen optical isomerides. In addition to cinchonine and cinchonidine, various other isomeric bases, made synthetically, have accordingly been described.

From cinchonine and cinchonidine identical β' -vinyl- α -quinuclidones have been obtained, which have equal optical rotations. It follows that both bases have

the same configurations at carbon atoms 1 and 2. On the other hand, the deoxy-compounds, which result from the replacment of the hydroxyl in cinchonine and cinchonidine by hydrogen are different from each other. Hence cinchonine and cinchonidine must differ in the configuration at carbon atom 3. The spatial arrangement at the fourth asymmetric carbon atom appears, on the other hand, to be the same in both bases. The alkaloids which differ from cinchonine and cinchonidine in the configuration of carbon atom 4 are called *epicinchonine* and *epicinchonidine*, respectively.

The melting point of cinchonidine is 207°; $[\alpha]_D = -111^\circ$ (alcohol).

HYDROCINCHONINE and HYDROCINCHONIDINE, $C_{19}H_{24}N_2O$. These two stereoisomeric alkaloids occur in cinchona bark, but only in very small quantities. They can, however, be readily obtained by the catalytic reduction of cinchonine and cinchonidine, respectively. They differ from these bases constitutionally in that they contain a saturated ethyl radical in place of the unsaturated vinyl group. They correspond therefore to the formula below. Configuratively, hydrocinchonine corresponds to cinchonine, and hydrocinchonidine to cinchonidine:



Neither compound decolorizes acidified potassium permanganate in the cold.

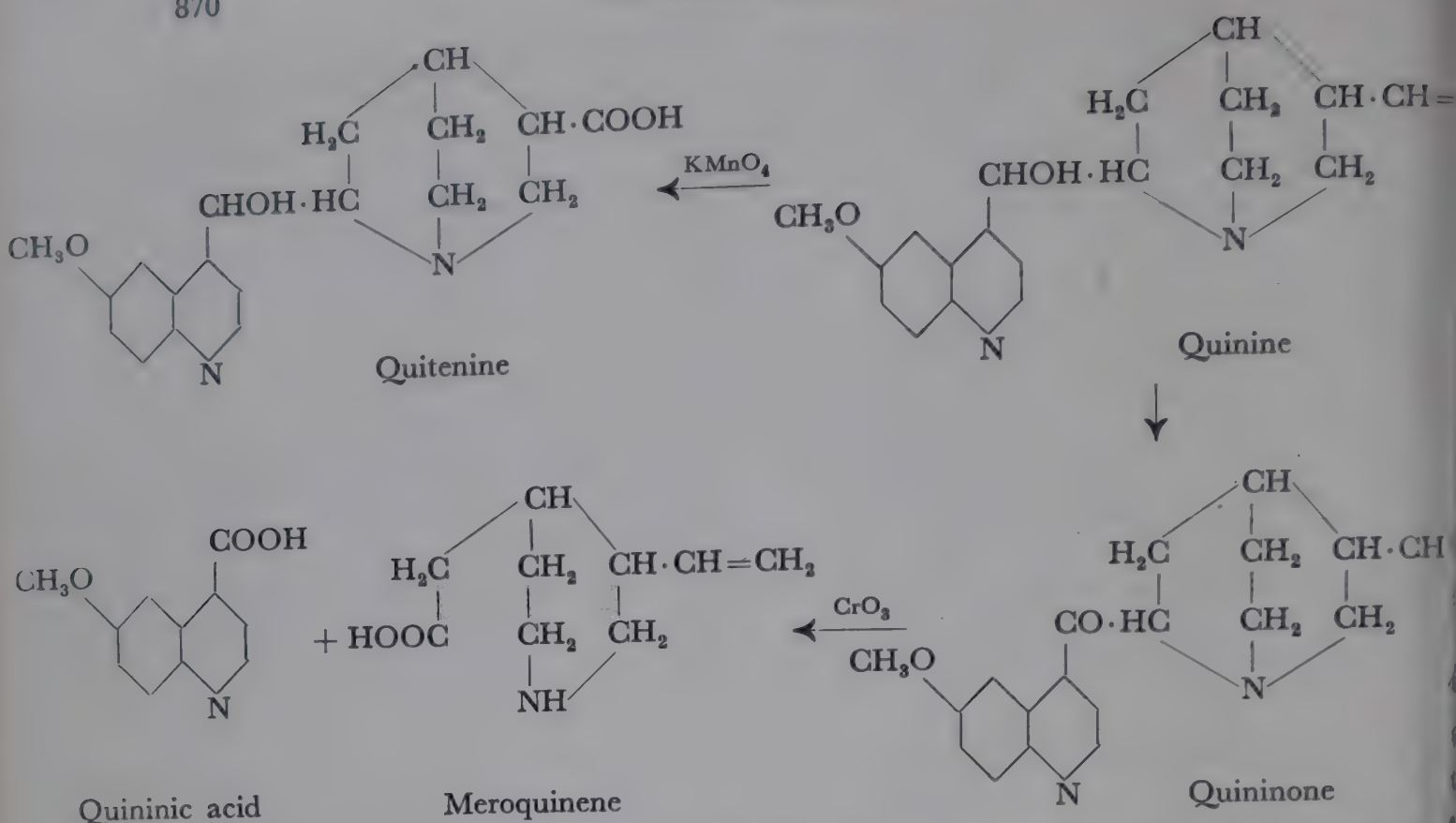
The melting point of hydrocinchonine (cinchotine) is 277° , $[\alpha]_{\text{D}} = +204^{\circ}$. The melting point of hydrocinchonidine is 229° , $[\alpha]_{\text{D}} = -98.5^{\circ}$.

If cinchonine and cinchonidine are oxidized to the ketones and the latter are reduced with hydrogen and palladium, two pairs of alcohols are formed: hydrocinchonine, *epi*hydrocinchonine, hydrocinchonidine, and *epi*hydrocinchonidine. The difference between the *epi*hydrocinchonine-hydrocinchonine pair (and likewise between the corresponding cinchonidine pair) arises out of their possessing opposite configurations at the asymmetric carbon atom 4, while the hydrocinchonine-hydrocinchonidine pair (and likewise the corresponding *epi* pair) differ from each other in their turn, as has already been explained, in the spatial arrangement about the third asymmetric carbon atom, but have the same configuration at the fourth.

Quinine, $C_{20}H_{24}N_2O_2$. This most important cinchona alkaloid was isolated from cinchona bark simultaneously with cinchonine by Pelletier and Caventou in 1820. It is contained in this source in considerable quantities. It is of great importance in medicine.

In chemical structure quinine is very closely related to cinchonine, being the methoxyl derivative of the latter. It therefore undergoes similar chemical transformations to cinchonine. The methoxyl group is in the *p*-position to the quinoline nitrogen (carbon atom 6).

Controlled oxidation with potassium permanganate leads to a carboxylic acid, *quitenine*, and careful acid oxidation to *quininone*, a ketone of the cinchoninone type. More powerful oxidation with chromic acid gives *meroquinene* (or, by further oxidation, cincholoiponic acid, loiponic acid), and *quininic acid*:



The constitution of quinonic acid, the only fission product which is different from the fission products of cinchonine, is established by its synthesis, which, starting with 6-methoxyquinoline, is carried out in a similar way to Kaufmann's synthesis of the corresponding cinchoninic acid, passing through 6-methoxy-4-cyanoquinoline (p. 867).

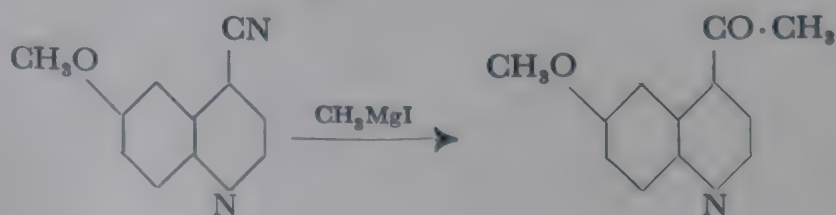
By means of amyl nitrite and sodium ethylate, quinone is decomposed into quinonic acid and the oxime of β' -vinyl- α -quinuclidone, and the latter agrees in all its properties with the substance prepared from cinchonine and cinchonidine. In a stereochemical sense, quinine and cinchonidine appear to correspond; likewise quinidine and cinchonine appear to be of identical configuration.

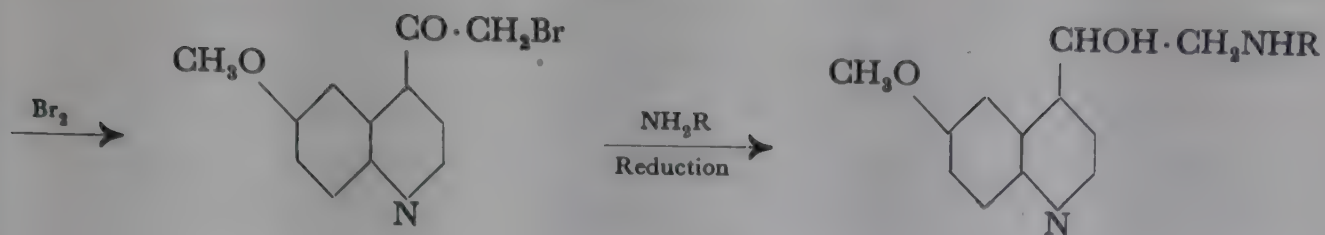
By heating with acids (acetic, phosphoric) quinine also undergoes a hydramine fission, rearranging into the isomeric *quinotoxine* or *quinicine*.

Anhydrous quinine melts at 177° ; the trihydrate at 57° ; $[\alpha]_D = -158.2^\circ$. Quinine dissolves only very slightly in water, better in ether, and still more readily in alcohol and chloroform. Aqueous solutions of the sulphate fluoresce blue.

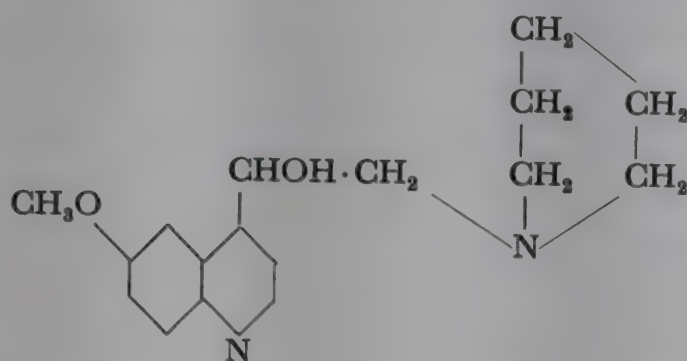
SYNTHETIC EXPERIMENTS IN THE QUININE SERIES. The importance of quinine in medicine has stimulated various syntheses with the object of making simpler compounds similar in action to quinine.

Thus A. Kaufmann made methoxyquinolyl alkyl ketones from 6-methoxy-4-cyanoquinoline and alkylmagnesium salts. These compounds were brominated, treated with amines, and finally reduced to carbinols:



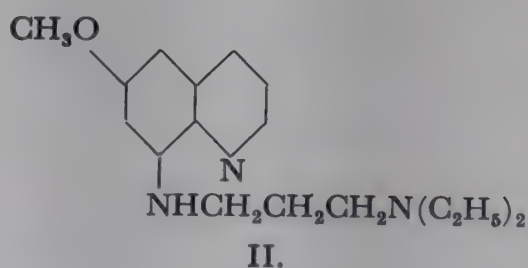
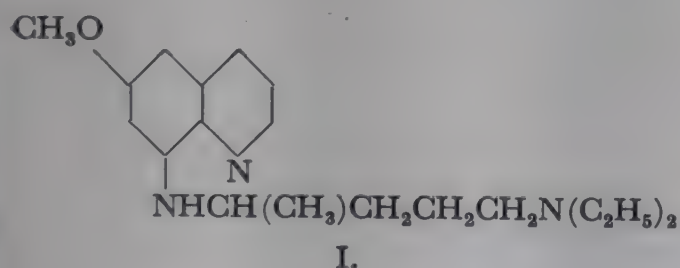


As a special example from this group the compound below, which shows certain analogies with quinine in structure, may be mentioned:

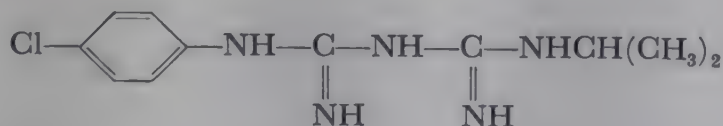


All these synthetic products have, however, proved to be very different from quinine in their pharmacological and physiological action, although resemblance in some way or other is not to be denied, e.g. in their toxic action on paramecia. They are, however, entirely without action in the treatment of malaria.

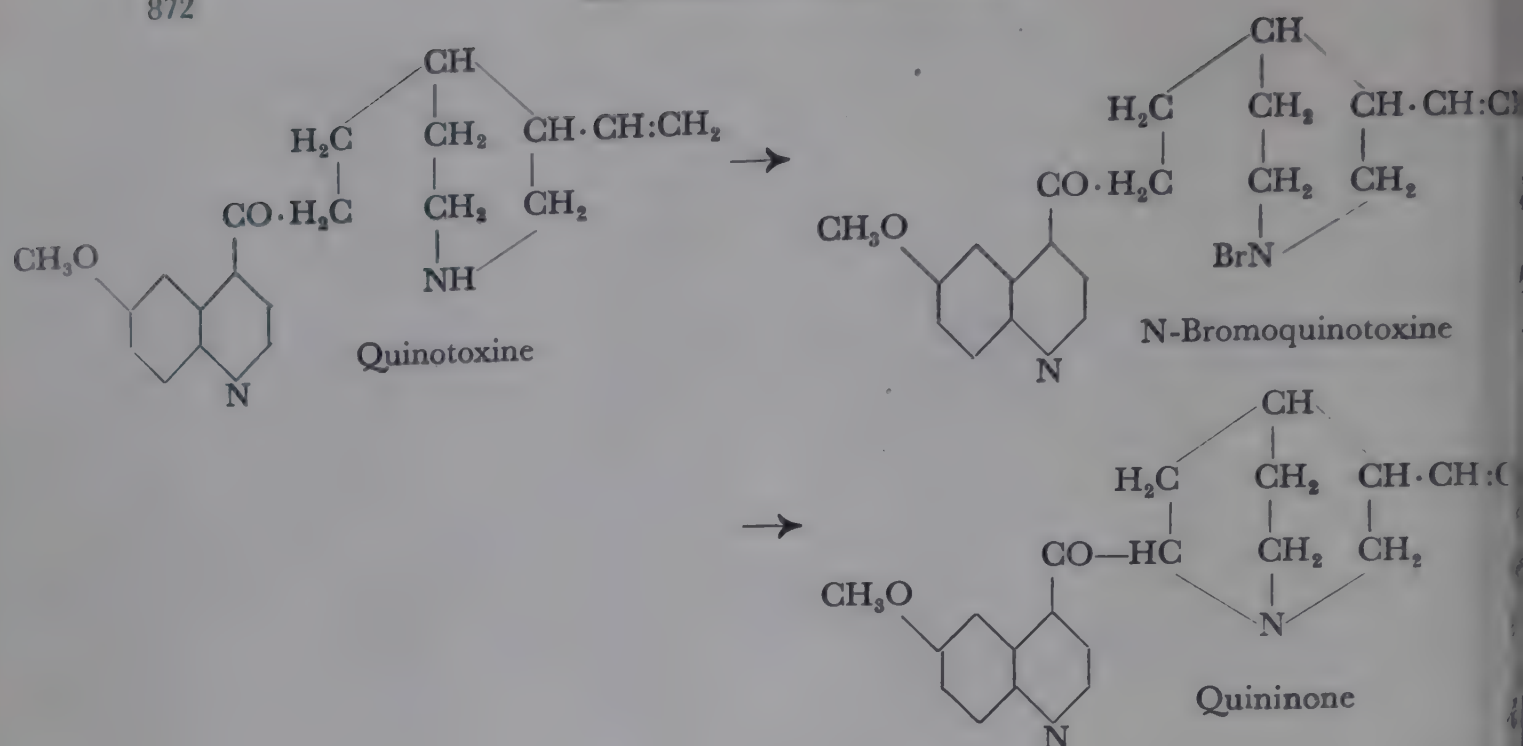
On the other hand, a quinoline derivative, the so-called *plasmoquin* (Pamaquin), has been found which is of use in malaria. It is 8-(diethylaminoisopentylamino)-6-methoxyquinoline (I). Related substances have a similar action, e.g. (II), and also 8-(γ -aminopropylamino)-6-ethoxyquinoline and 8-(δ -aminobutylamino)-6-ethoxyquinoline (see also *atebrin*, p. 633).



Another effective antimalarial, *Paludrine*, which is widely used nowadays, has a completely different structure, being a biguanide derivative of the formula:

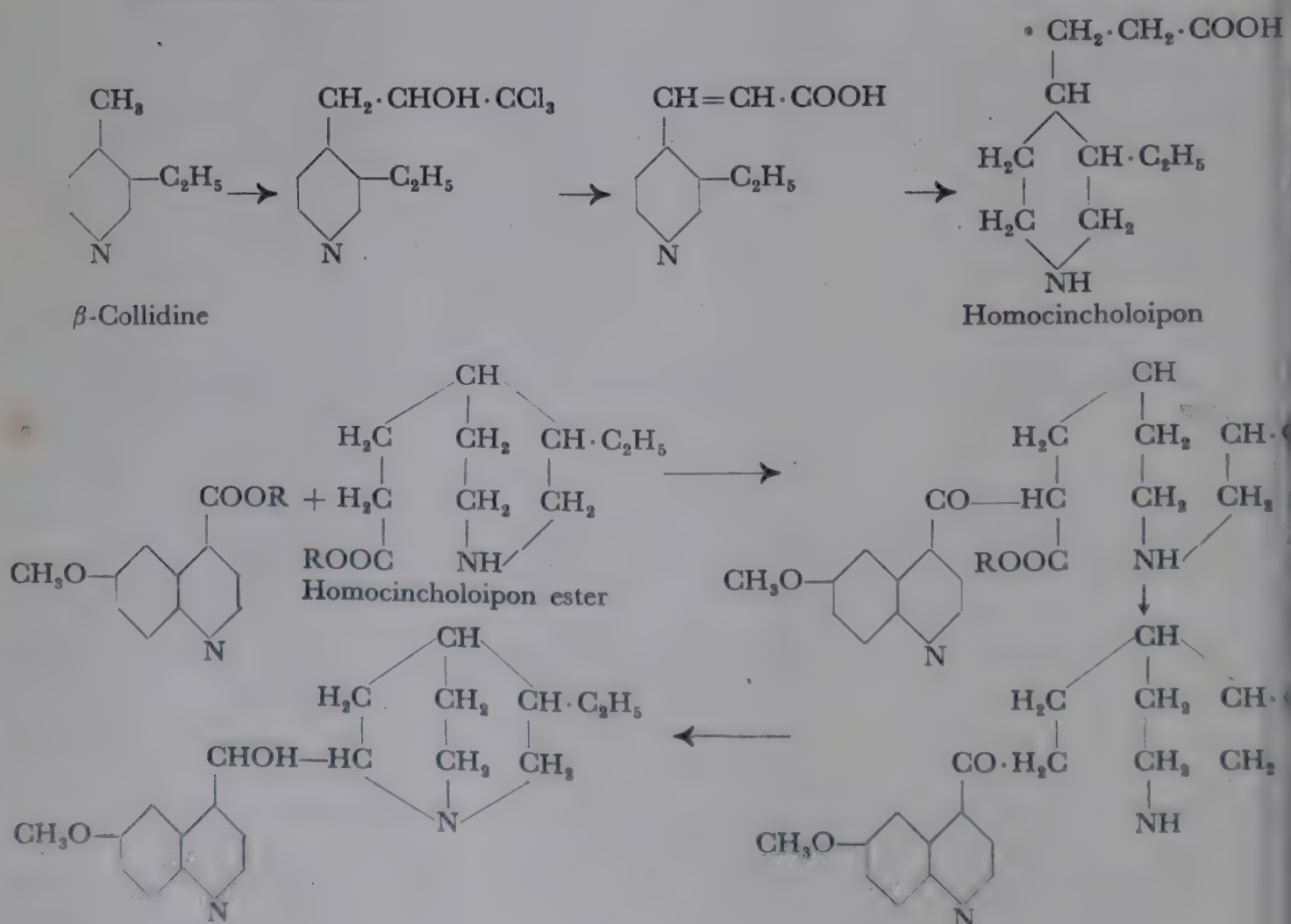


Rabe and his co-workers have carried out successful experiments on the partial synthesis of quinine. First they succeeded in converting quinotoxine into N-bromoquinotoxine by means of sodium hypobromite. Sodium ethylate removed hydrogen bromide from this compound. The quinone formed was readily reduced to quinine:



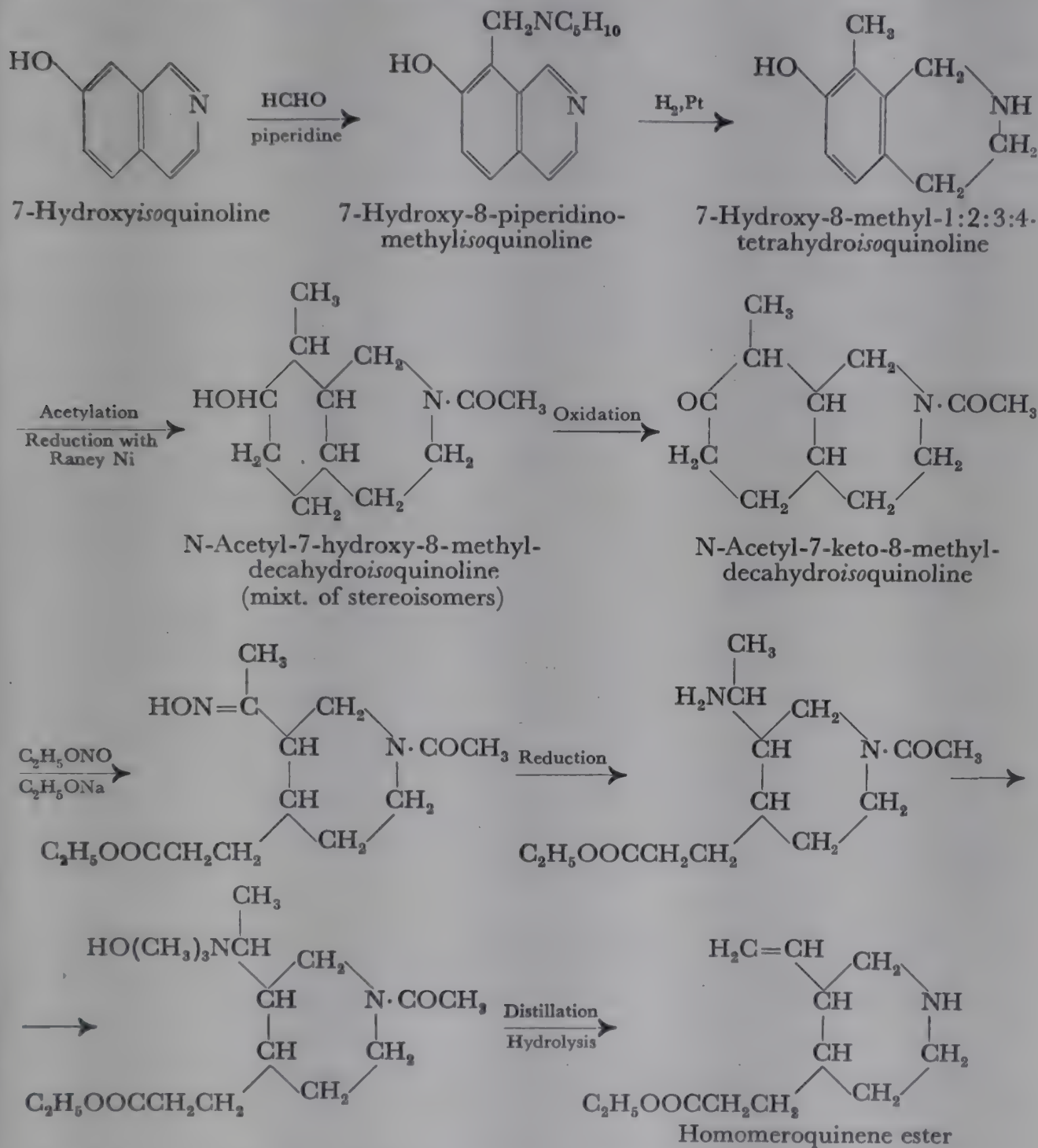
Dihydroquinotoxine and dihydroquinine have been synthesized by P. Rabe in the following way:

β -Ethyl- γ -methylpyridine (β -collidine) was condensed with chloral, the reaction product (chloral-collidine) hydrolysed to β -(β' -ethyl- γ' -pyridyl)-acrylic acid, and this was reduced by sodium and alcohol to homocincholoipon. The latter can be combined with quininic ester to dihydroquinotoxine and this converted into dihydroquinine through the N-bromo-derivative:



The homocincholoipon which Rabe used was previously resolved into its optically active forms by means of the tartrate. The synthesis thus gave optically active dihydroquinine ($[\alpha]_D^{18} = -140.4^\circ$, alcohol), which agreed with that obtained from natural quinine as regards optical rotation and its other properties.

More recently quinine itself has also been synthesized. The problem consisted in the synthesis of *homomeroquinene*, which was the essential intermediate sought for the synthetic preparation of quinine. This homomeroquinene has been built up by R. B. Woodward and W. E. Doering in the following way:



The N-benzoyl derivative of this homomeroquinene ester was condensed with quininic ester, by the method of Rabe described above, thus giving quinine.

PHARMACOLOGICAL ACTION OF QUININE. The most valuable property of quinine is its rapid lethal action on malaria organisms. It is to this that it owes its outstanding position in medicine for the treatment of malaria, and as a prophylactic. The temperature of the body in fever is lowered by quinine. Bactericidal action is a characteristic property of quinine, but it is inferior to that

of many quinine homologues (cf. the section on cupreine, below), and it plays almost no part in its antimalarial action. Small doses of quinine stimulate the voluntary muscles, and temporarily increase the capacity of the body for work. This property of cinchona bark was known even to the South American aborigines and was put to practical use by them.

Quinidine, $C_{20}H_{24}N_2O_2$. Quinidine bears the same relationship to quinine as cinchonine does to cinchonidine (cf. p. 870). The bases are stereoisomeric. They agree in the configuration of the asymmetric carbon atoms 1 and 2, and differ in the spatial arrangement at the asymmetric carbon atom 3.

The melting point of quinidine is 171.5° ; $[\alpha]_D = +243.5^\circ$.

HYDROQUININE and **HYDROQUINIDINE**, $C_{20}H_{26}N_2O_2$. These two alkaloids contain an ethyl radical in place of the vinyl group in the quinuclidine moiety; in other respects they correspond to quinine and quinidine respectively, from which they can be obtained by catalytic reduction. They react towards potassium permanganate as saturated substances.

Hydroquinine melts at 172° (anhydrous); $[\alpha]_D = -142^\circ$ (alcohol).

Hydroquinidine melts at $166-167^\circ$. It is dextrorotatory.

Cupreine, $C_{19}H_{22}N_2O_2$. This alkaloid was discovered in the bark of a species of *Remijia*, in which it occurs in small quantities. It is 6-hydroxycinchonine or demethylated quinine. It can be converted into quinine by methylation.

It crystallizes with two molecules of water of crystallization, and melts when anhydrous at $201-202^\circ$; $[\alpha]_D = -174.4^\circ$ (alcohol).

If the hydrogen atom of the phenolic hydroxyl group of cupreine is replaced by other alkyl radicals, homologues of quinine are formed (*quinethyline*, *quin-propyline*, etc.) which show a very similar pharmacological action to quinine, and are in some cases even more active (Grimaux and Arnaud).

HYDROCUPREINE is relatively easily obtained by demethylation of hydroquinine. The removal of the methyl group can be brought about by heating with hydrochloric acid at 150° . Various alkyl ethers of dihydrocupreine have excited interest on account of their disinfecting and bactericidal action (Morgenroth). *Ethyl-dihydrocupreine* (optochine) is used in the treatment of pneumococcal infections and an eye disease (*Ulcus corneæ serpens*), *isoamyl-dihydrocupreine* (eucupine) and *isooctyl-dihydrocupreine* (vuzine) are used as antiseptics, but opinions differ regarding the value of these preparations.

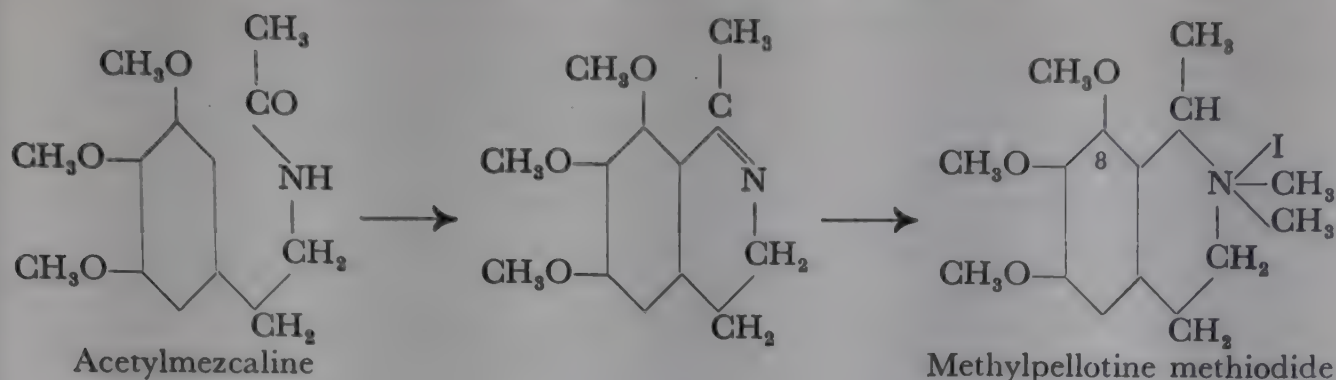
CHAPTER 69

ALKALOIDS WITH AN ISOQUINOLINE RING

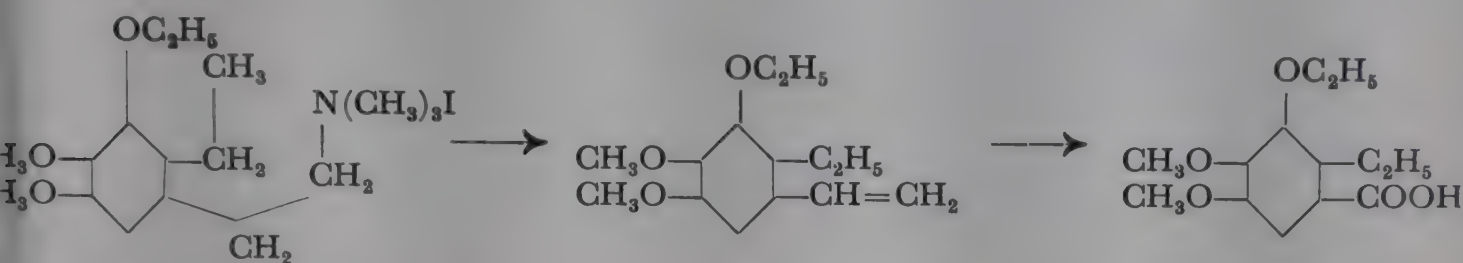
1. Anhalonium alkaloids. Salsoline

In addition to *mezcaline* (see p. 841) and *hordenine* (see p. 841) which have already been dealt with, yet another series of bases is found in various species of *Anhalonium* (cacti), which were recognized as *isoquinoline* derivatives (Späth). To this class belong among others:

Pellotine, $C_{13}H_{19}NO_3$. This base contains two methoxyl groups, a phenolic hydroxyl, and a NCH_3 group. Its constitution is known. Acetylmezcaline can be converted into an *isoquinoline* derivative by means of phosphorus pentoxide, which, after reduction and methylation, gives a methiodide which proves to be identical with methylpellotine methiodide:



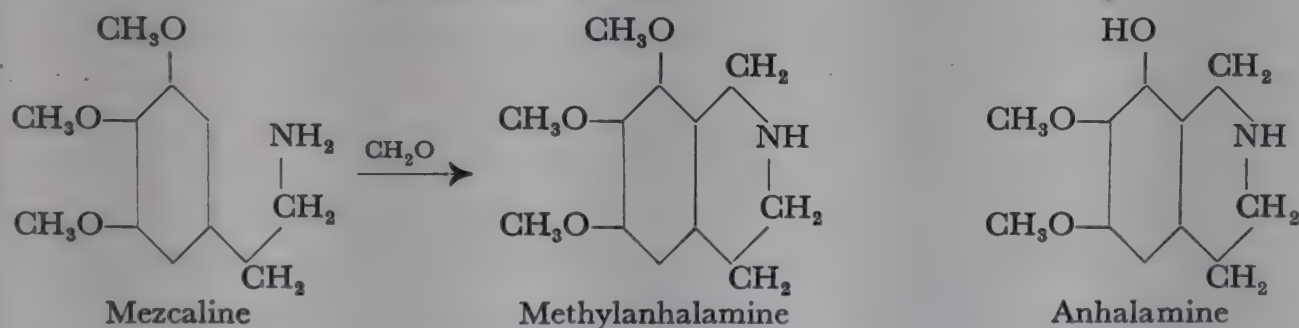
The constitution of pellotine is thus settled except for the position of the free phenolic group. This is in position 8 since O-ethylpellotine can be degraded to the following compounds:



whose constitutions have been unequivocally established. The alkaloid melts at 110° .

Anhalonidine, $C_{12}H_{17}NO_3$, is, in contrast to pellotine, a secondary base; it also contains two methoxyl groups. Completely methylated anhalonidine is identical with methypellotine methiodide. The base differs from pellotine in constitution only in that there is no methyl group attached to nitrogen.

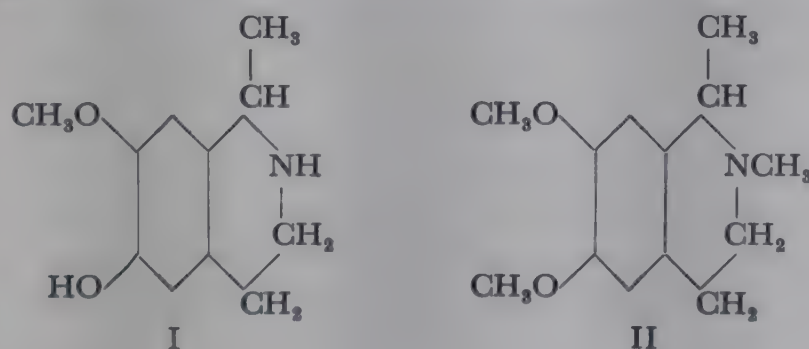
Anhalamine, $C_{11}H_{15}NO_3$ (m.p. 185°). Methylanhalamine is formed by the condensation of mezcaline with formaldehyde:



The constitution of anhalamine, with the exception of the position of the free phenolic group (the alkaloid contains only two methoxyl groups) is thus made clear. The phenolic group was ascertained to be in position 8.

Methylanhalamine is identical with *anhalinine*, another alkaloid obtained from various species of *Anhalonium*.

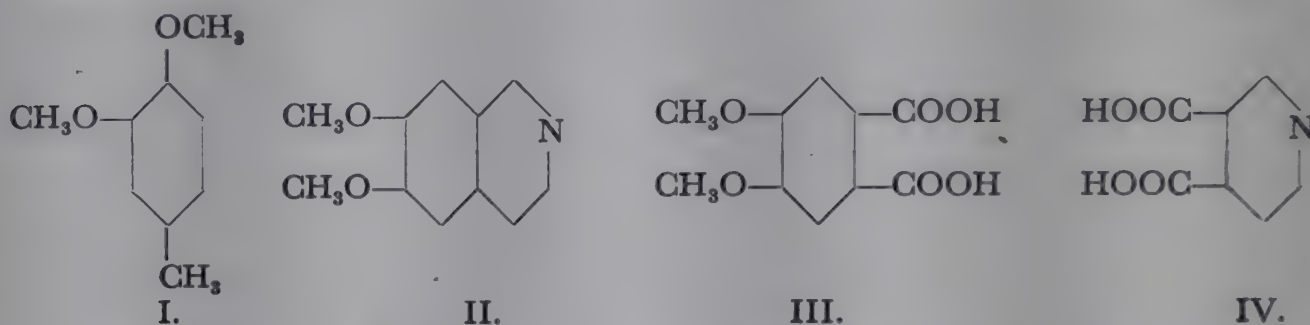
Salsoline, from *Salsola Richteri*, is closely related in constitution to the anhalonium alkaloids. It has formula I. O,N-Dimethylsalsoline (II) proved to be identical with the alkaloid *carnegine*.



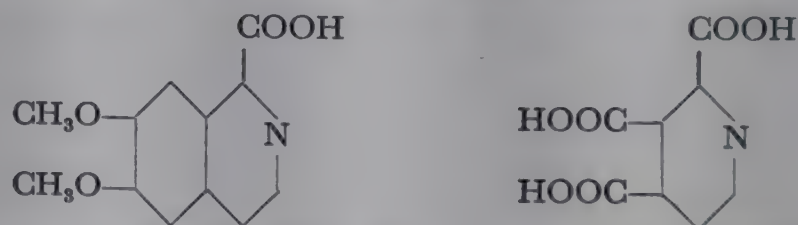
2. Papaverine group

This group comprises a series of related *isoquinoline* bases, of which many, such as *papaverine*, *laudanosine*, *laudanine*, *laudanidine*, *narcotine*, *narceine*, etc., occur in opium, and others, particularly *hydrastine*, occur in varieties of *Hydrastis*. They all belong to the same type, being substituted benzyl*isoquinoline* derivatives.

Papaverine, $C_{20}H_{21}NO_4$. The fusion of papaverine with alkali has furnished the most important results with regard to the elucidation of its constitution (Goldschmiedt). The alkaloid breaks down into *homoveratrole* (I) and *dimethoxyisoquinoline* (II). The structure of the latter emerges unequivocally from its oxidative degradation, which leads partly to *metahemipinic acid* (III) and partly to *cinchomeronic acid* (IV):

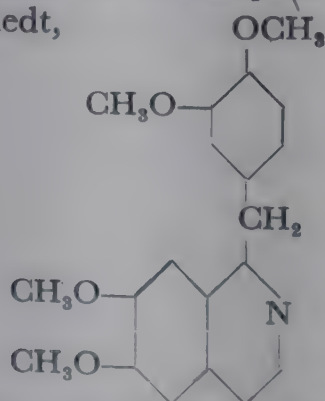


The two fission products, homoveratrole and dimethoxy*isoquinoline*, together with the empirical formula of the alkaloid, characterize papaverine as a dimethoxybenzyl-dimethoxy*isoquinoline*. Oxidative degradation of the alkaloid with permanganate shows definitely where the two halves of the molecule are linked. Together with various other products of oxidation, 6:7-dimethoxy*isoquinoline*-1-carboxylic acid and α -carboxycinchomeronic acid are formed:



Dimethoxy*isoquinoline*-1-carboxylic acid α -Carboxycinchomeronic acid

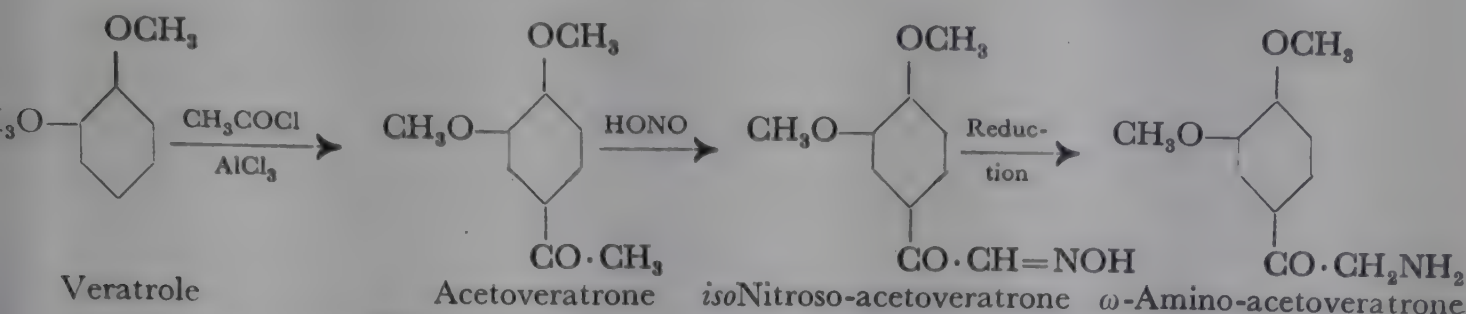
Hence the dimethoxybenzyl moiety in papaverine must be attached to the *isoquinoline* half in the 1-position of the *isoquinoline* nucleus. This structural formula, derived by Goldschmiedt,



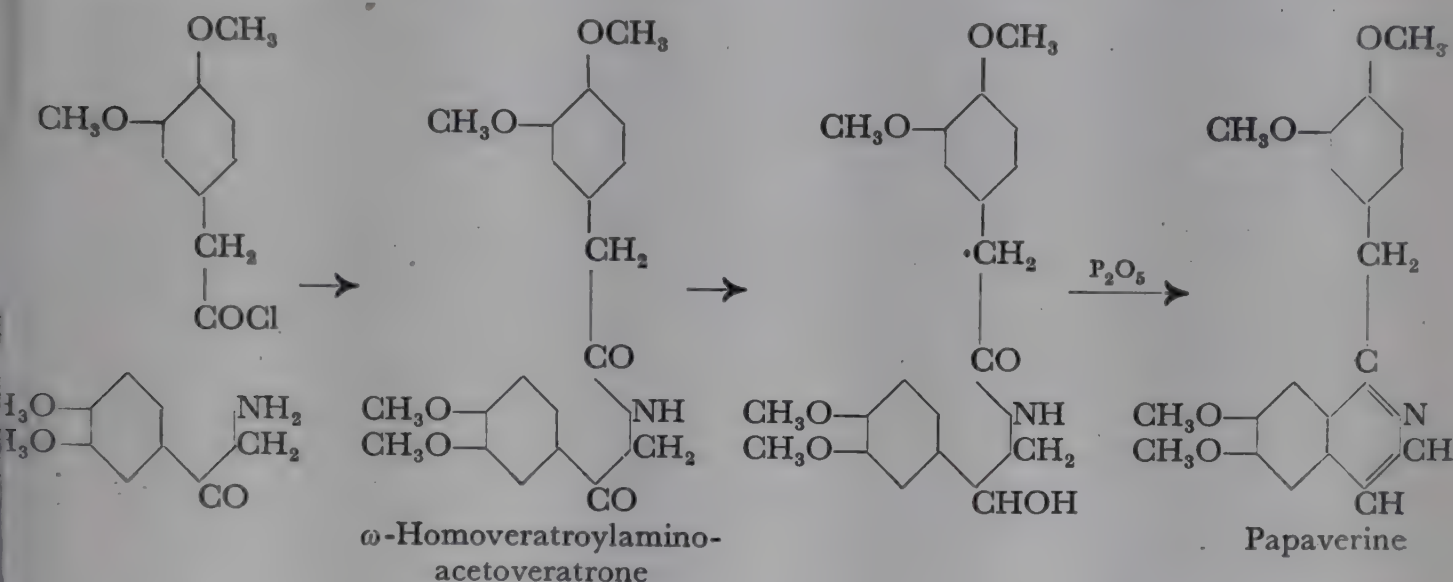
Papaverine, 1-(3':4'-Dimethoxybenzyl)-
6:7-dimethoxy*isoquinoline*

has been confirmed by all further investigations, especially by the straightforward synthesis of papaverine by A. Pictet and Gams.

For this, ω -amino-acetoveratrone and homoveratroyl chloride were used. The first is obtained, for example, as follows:



The action of homoveratroyl chloride on ω -amino-acetoveratrone gives ω -homoveratroylamino-acetoveratrone. Sodium amalgam reduces this to the corresponding alcohol. If the latter is boiled with phosphorus pentoxide in xylene solution, water is eliminated, and ring closure occurs with the formation of an *isoquinoline* type, papaverine:



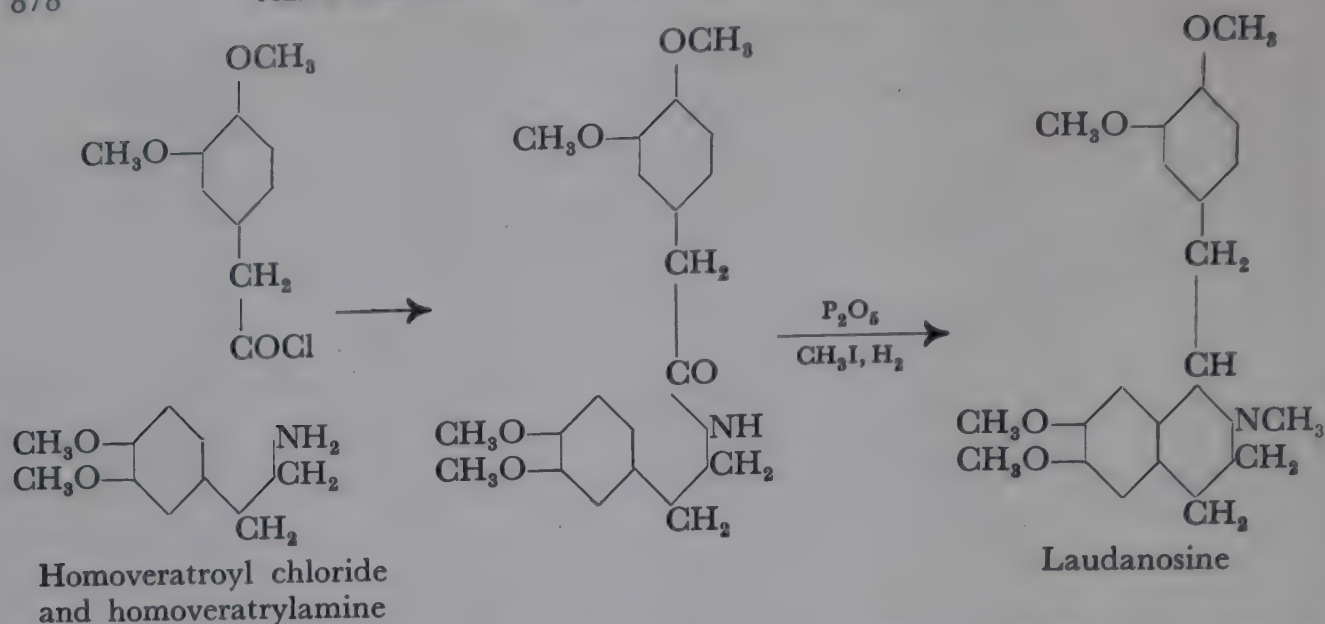
Papaverine was isolated from opium in 1848 (Merck). It melts at 147° , is optically inactive, and is almost insoluble in water, but readily soluble in chloroform. In its physiological action it resembles morphine and codeine. It has a narcotic action, weaker however than morphine, but, on the other hand, it has a tetanizing action, recalling codeine in this respect.

Laudanosine, $\text{C}_{21}\text{H}_{27}\text{NO}_4$. This base occurs in small quantities in opium. It is very closely connected, as regards constitution, with papaverine, of which it is the N-methyl-tetrahydro-derivative. It can therefore be obtained (as the racemate) by the reduction of papaverine methochloride.

The racemic compound can be resolved into its optically active forms by means of its salt with quinic acid. The dextrorotatory form is identical with naturally occurring laudanosine.

The alkaloid has been totally synthesized by A. Pictet. Homoveratroylamine is acylated with homoveratroyl chloride. Phosphorus pentoxide eliminates water from the condensation product, giving dihydropapaverine through ring-closure to the *isoquinoline* ring. This can, on the one hand, be oxidized to papaverine (second synthesis of papaverine), or on the other reduced to *dl*-laudanosine via the methochloride:

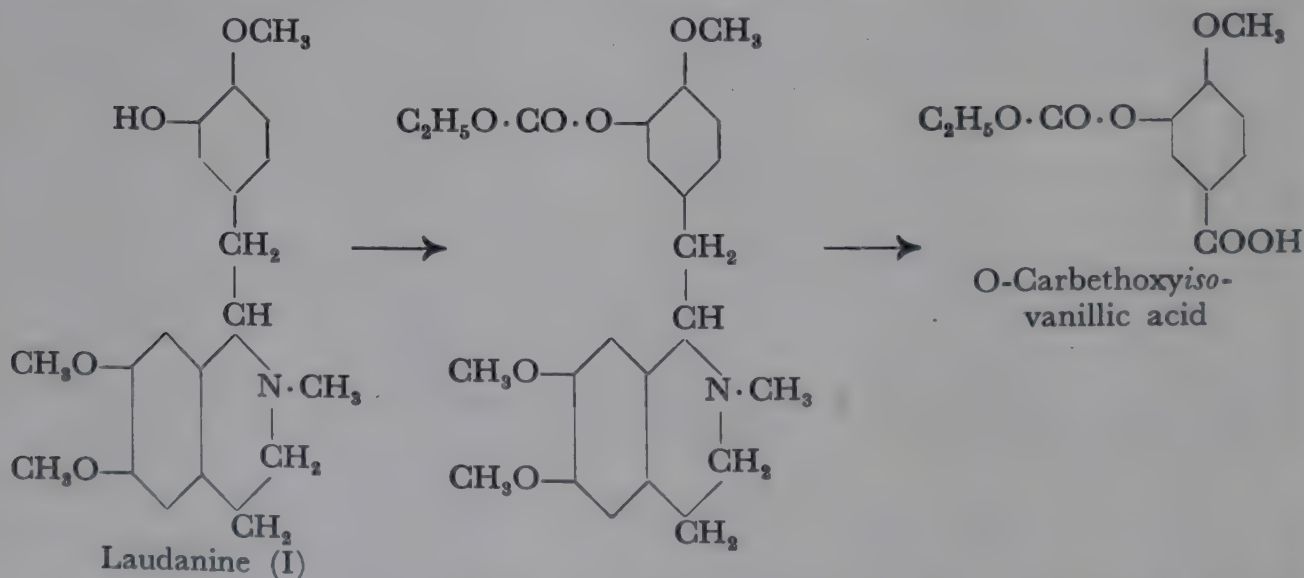
ham



d-Laudanosine melts at 89°. In hydrochloric acid $[\alpha]_D^{22} = +108.4^{\circ}$ ($c = 2\%$). It produces tetanus and is considerably more poisonous than papaverine.

Laudanine, $C_{20}H_{25}NO_4$. Laudanine is closely related constitutionally to laudanosine, from which it differs only in that it has one of the four phenolic methoxyl groups demethylated. Consequently it is readily converted into *dl*-laudanosine by means of diazomethane.

The investigations of Späth indicate which of the four hydroxyl groups is not methylated. The O-carbethoxy-derivative of laudanine can be degraded by oxidation to carbethoxyisovanillic acid, and laudanine ethyl ether to O-ethylisovanillic acid. Hence laudanine must have the formula I:



It has been possible to prepare laudanine synthetically by a route similar to that depicted above for laudanosine. The starting substances in this case are O-carbethoxy-homoisovanilloyl chloride and homoveratrylamine.

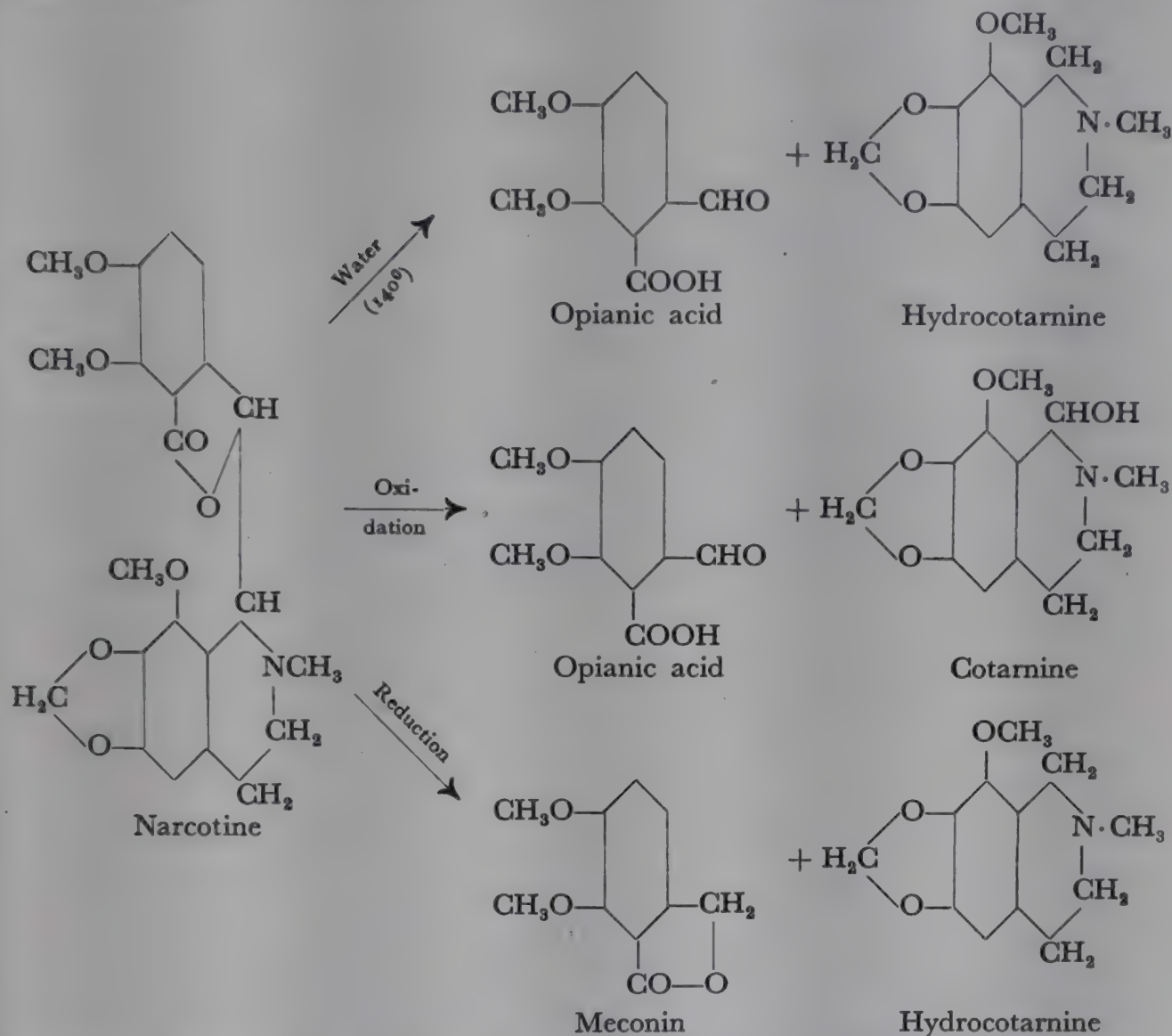
Laudanine melts at 166°. It is optically inactive. It is soluble in alkalis and in chloroform.

Laudanidine, $C_{20}H_{25}NO_4$, is the laevorotatory form of laudanine corresponding with it in nearly all reactions.

Narcotine, $C_{22}H_{23}NO_7$. Narcotine is one of the chief alkaloids of opium, in which it occurs up to the extent of about 10%. It was discovered by Robiquet in 1817.

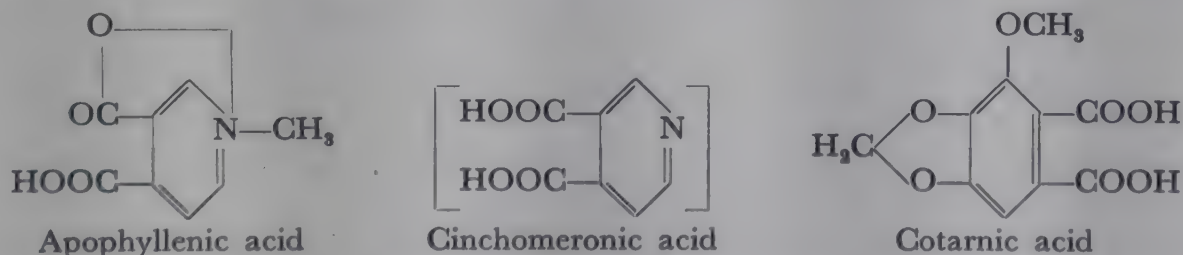
An important fact in connection with the determination of the constitution

of narcotine is that it is easily broken down in various ways into two fission products. Water at elevated temperatures (about 140°) breaks it down into *opianic acid* (which is further reduced to meconin) and *hydrocotarnine*, oxidizing agents (nitric acid, chromic acid, etc.) produce *opianic acid* and *cotarnine*, and reducing agents (zinc and hydrochloric acid, sodium amalgam) produce *meconin* and *hydrocotarnine*:



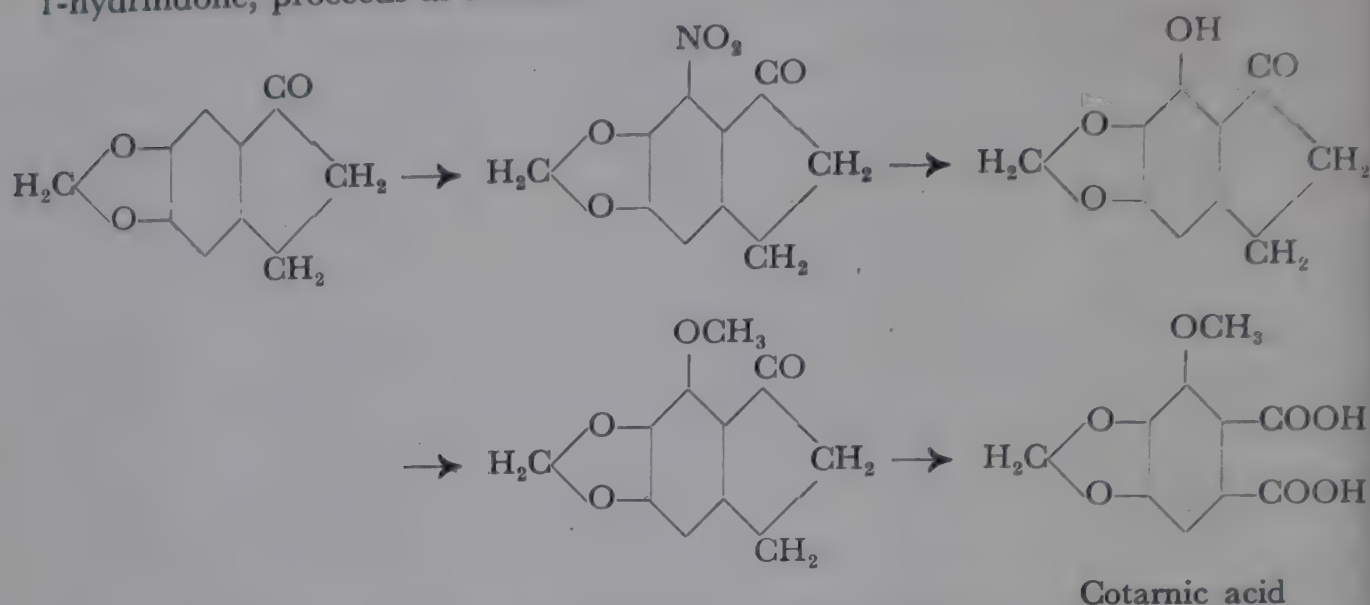
To elucidate the constitution of narcotine it is therefore necessary in the first place to determine the structures of cotarnine and opianic acid.

COTARNINE, $C_{12}H_{15}NO_4$. By oxidative degradation of cotarnine, *apophyllenic acid* (i.e. the methyl betaine of cinchomeronic acid), or *cotarnic acid* (a derivative of phthalic acid), is obtained, according to the choice of oxidizing agent. Thus is cotarnine seen to be an *isoquinoline* derivative:

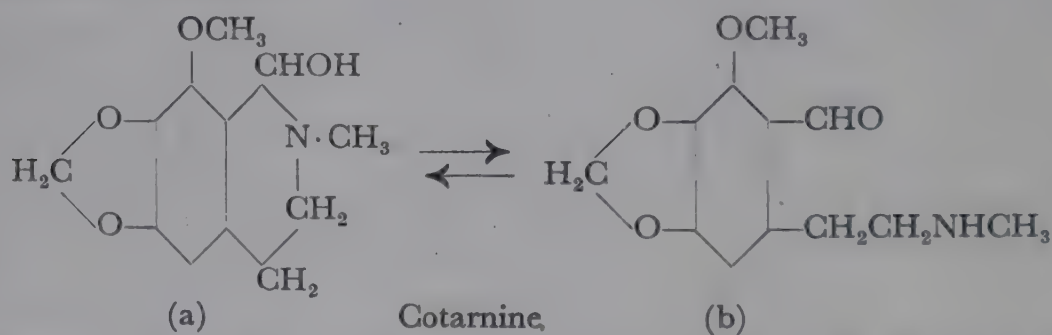


The above formula for cotarnic acid is supported by its analysis and by its degradation to gallic acid (by means of hydriodic acid), and substantiated by a

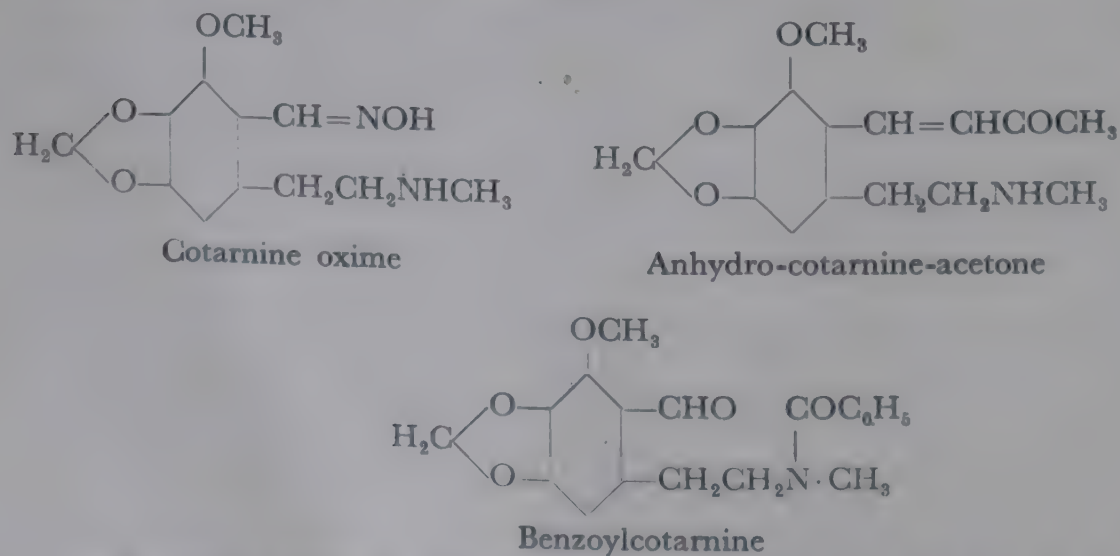
synthesis (Perkin, Robinson, Thomas) which, starting from 5:6-methylenedioxy-1-hydrindone, proceeds as follows:



In connection with the assessment of the constitution of cotarnine, it is furthermore essential to note that the substance displays aldehydic properties. It forms an oxime, and reacts with reactive methylene compounds, and with acetone, with elimination of water. These properties, together with the known constitution of apophyllenic acid and cotarnic acid show that cotarnine can only possess the two tautomeric formulæ:

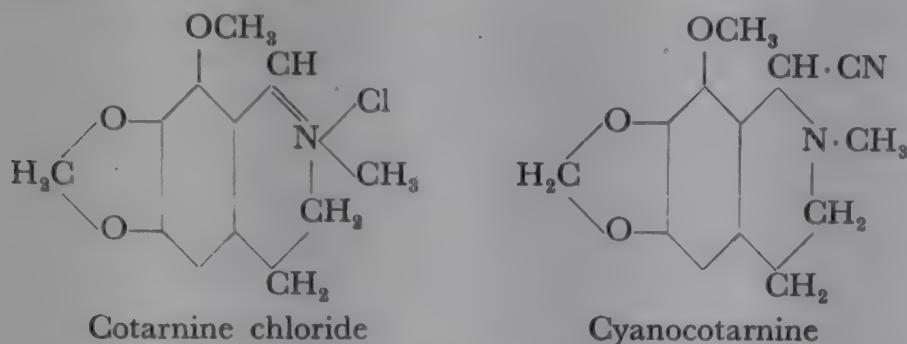


Cotarnine can, in fact, react either according to the cyclic formula (a) or the open formula (b). The latter readily explains the formation of the oxime, anhydrocotarnine-acetone, and a N-benzoylcotarnine:

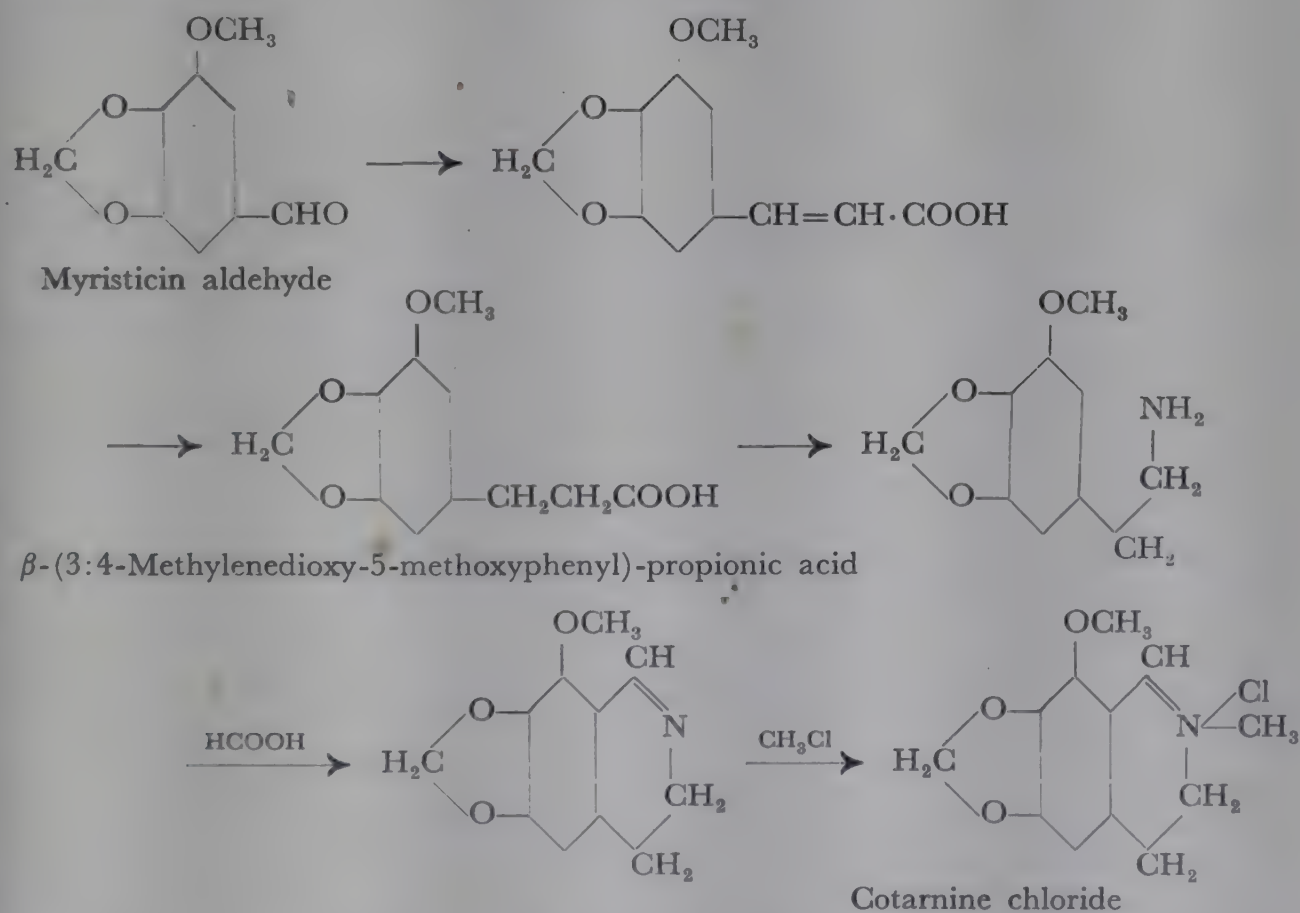


The cyclic formula affords an explanation for the fact that the salts of

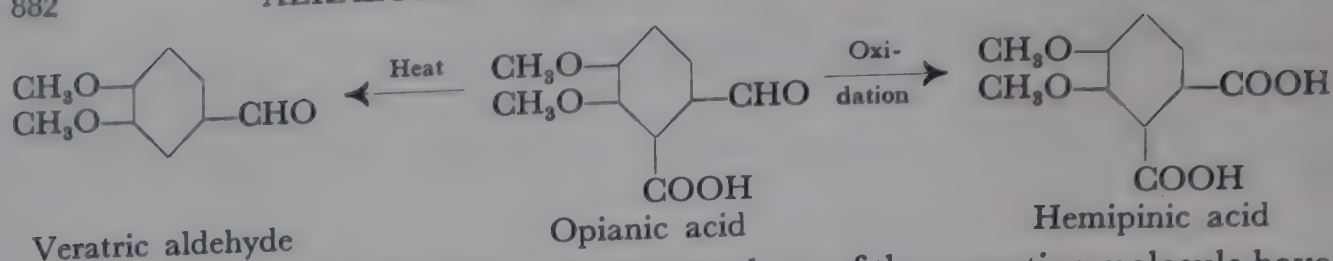
cotarnine with mineral acids are formed with elimination of water, and that, with potassium cyanide, a cyanocotarnine is formed in which, judging from its overall behaviour, the cyanide radical is linked to carbon, but which can, possibly, also react in a tautomeric form:



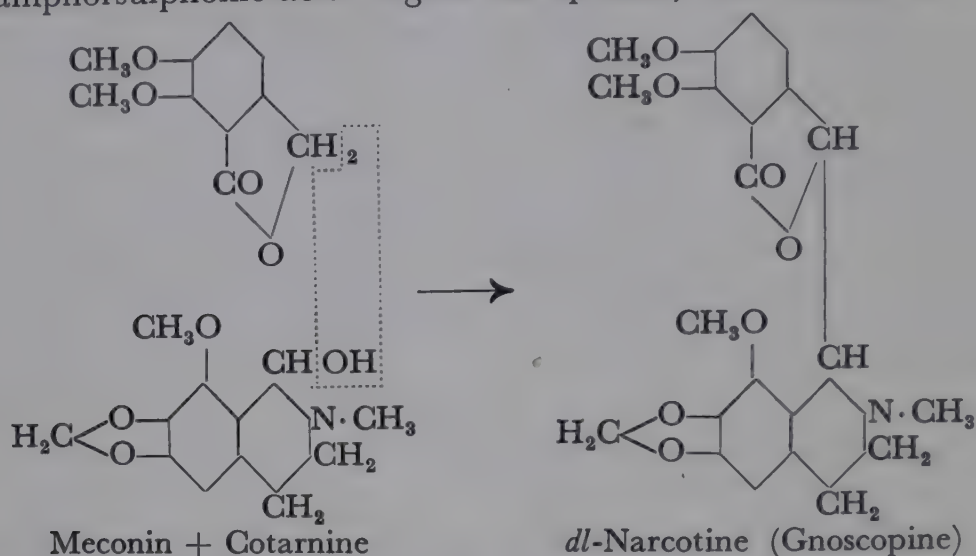
Finally, cotarnine has been synthesized by methods which confirm the constitution of the substance which was inferred from the degradation reactions. Thus, Decker condensed myristicin aldehyde with sodium acetate and acetic anhydride to give the corresponding cinnamic acid derivative, from which β -(3:4-methylenedioxy-5-methoxyphenyl)-propionic acid was obtained by reduction. This was converted into (3:4-methylenedioxy-5-methoxyphenyl)-ethylamine, via the amide, and the amine was converted into the dihydroisoquinoline derivative by means of formic acid. The methochloride of this was identical with cotarnine chloride:



OPIANIC ACID, $\text{C}_{10}\text{H}_{10}\text{O}_5$. The second fission product of narcotine contains no nitrogen, but has two methoxyl groups, an aldehyde group, and a carboxyl group. On heating, it loses carbon dioxide and gives veratric aldehyde. On oxidation, it yields hemipinic acid. Its constitution is thus established:



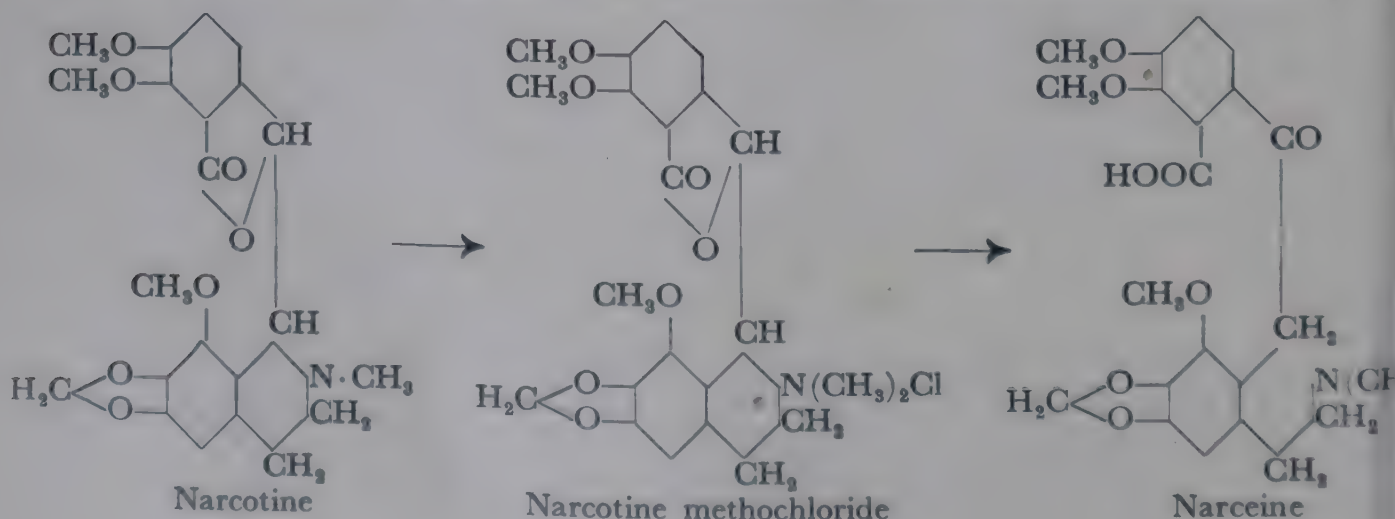
NARCOTINE. Now that the two fission products of the narcotine molecule have been examined we will return to the alkaloid itself. Its formula follows readily from the constitutions of cotarnine and opianic acid or meconin. The formula depicted below is thus derivable. This is further supported by a simple, smooth synthesis which was effected by Perkin and Robinson. Meconin and cotarnine react in equimolecular quantities with elimination of water to give *dl*-narcotine. This also occurs in opium, and is called *gnoscopine*. It can be resolved by means of bromocamphorsulphonic acid to give the optically active narcotics:



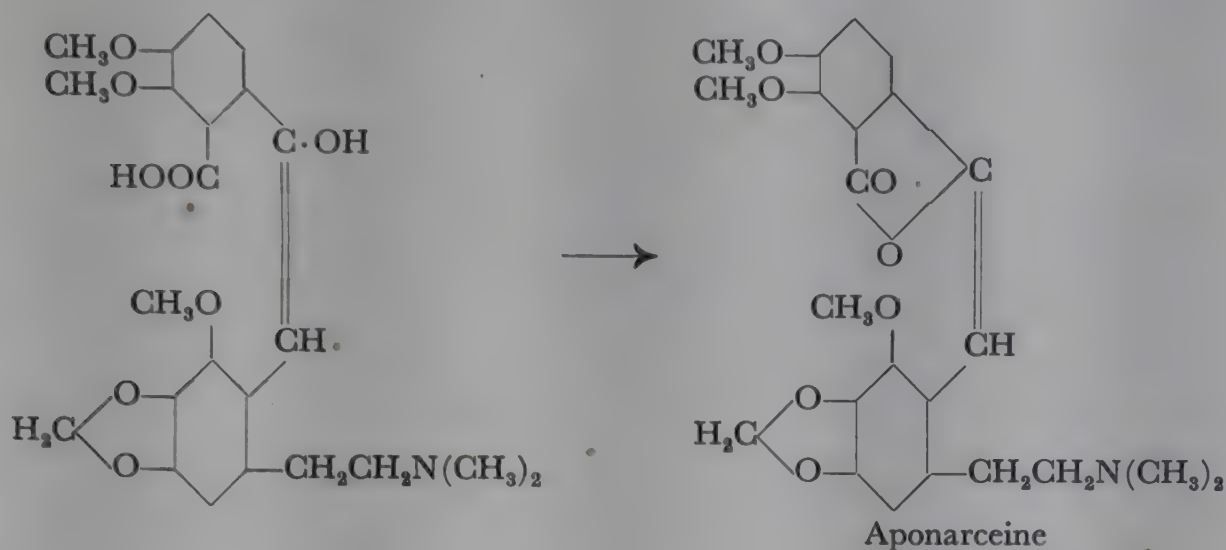
Narcotine melts at 176° , $[\alpha]_D = -200^{\circ}$ (chloroform). In hydrochloric acid solution it is dextrorotatory. It is very slightly soluble in water. Physiologically, narcotine behaves very much like morphine. Like the latter it is a narcotic, but is rather weaker.

Cotarnine melts at 133° . It is readily soluble in alcohol and ether, but with difficulty in water. It has hæmostatic and oxytocic action and is therefore used in medicine, particularly in gynæcology. It paralyses the central nervous system.

Narceine, $C_{23}H_{27}NO_8 + 3H_2O$. The opium alkaloid narceine is connected with narcotine, being the product of a simple transformation; it is formed from the latter by boiling the methochloride with alkali. This process is a hydramine fission, which we have already encountered in connection with ephedrine (conversion into phenyl ethyl ketone) and cinchonine (conversion into cinchotoxine):



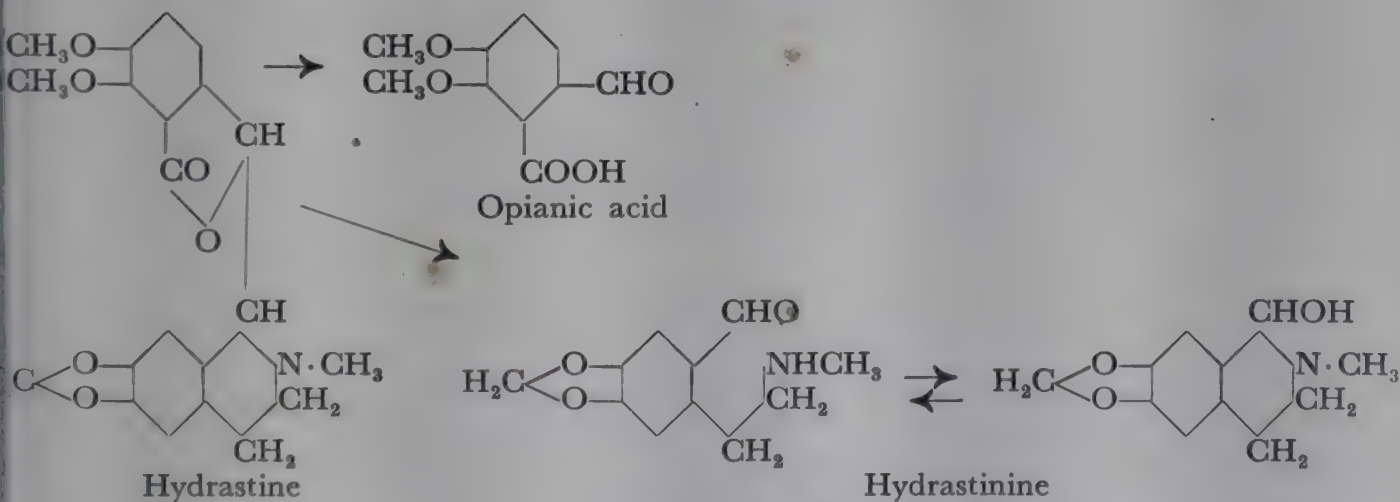
That there is a free carboxyl group in narceine is shown by the formation of esters and an amide. The existence of an oxime shows that the molecule contains a keto-group. Narceine loses water on heating with phosphorus oxychloride, and forms a lactone, *aponarceine*:



Narceine melts at 145° (the hydrated form melts at $170\text{--}171^\circ$). In non-toxic doses it has no marked physiological action.

Hydrastine, $\text{C}_{21}\text{H}_{21}\text{NO}_6$. Hydrastine is structurally very closely related to narcotine. It does not occur however, like the latter, in opium, but in the rhizomes of *Hydrastis canadensis*.

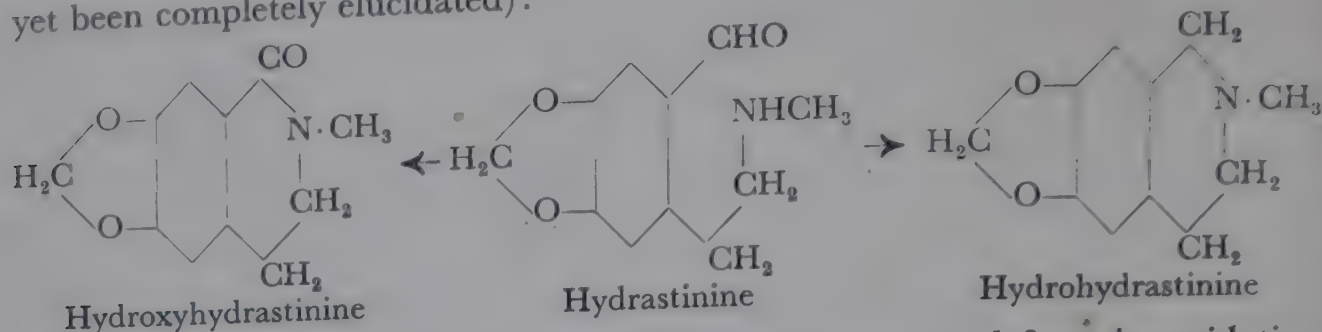
Oxidation with potassium permanganate or nitric acid cleaves it into *opianic acid* and *hydrastinine*. We have already discussed the constitution of opianic acid. Hydrastinine is related to cotarnine, and differs from the latter only in not possessing the methoxyl group:



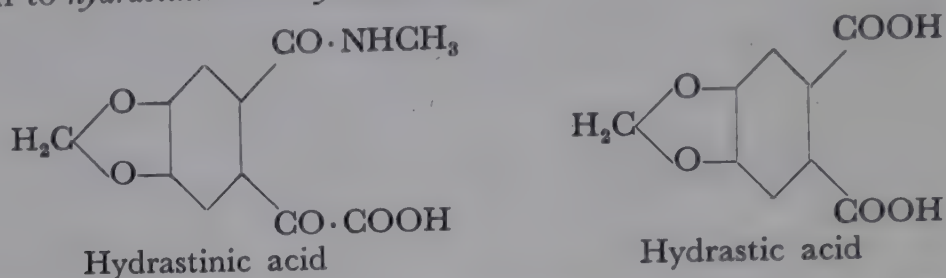
Like cotarnine, hydrastinine forms salts with elimination of water, and reacts according to two tautomeric formulæ, the cyclic *isoquinoline* form and the open aldehyde form. It also shares with cotarnine the property of combining with reactive methylene- and methyl-compounds to give anhydro-bodies (e.g. anhydrohydrastinine-acetone).

That hydrastinine is of aldehydic nature is also shown by the fact that when boiled with alkali it undergoes the Cannizzaro reaction, being converted into equal parts of the products hydroxyhydrastinine and hydrohydrastinine, of higher

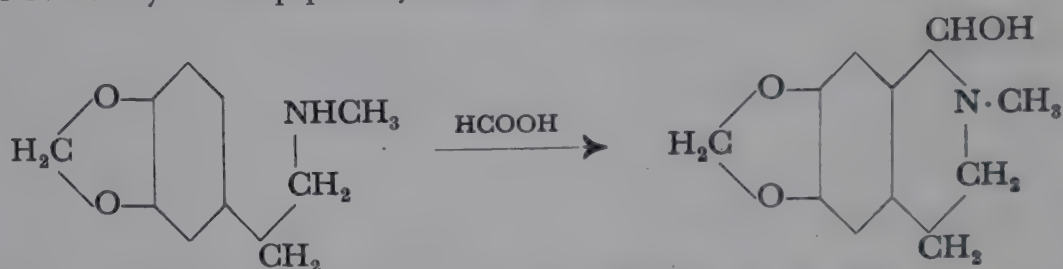
and lower state of oxidation respectively (the mechanism of the reaction has not yet been completely elucidated):



Knowledge of the constitution of hydrastinine emerged from its oxidative degradation to *hydrastinic* and *hydrastic acids*:



and also by various syntheses, one of which, for example, makes use of the condensation of N-methyl-homopiperonylamine with formic acid:



(For the degradation of berberine to hydrastinine, see p. 886).

Hydrastine melts at 132° ; $[\alpha]_D = -49.8^{\circ}$ (alcohol). Hydrastinine is optically inactive. M.p. $116-117^{\circ}$.

PHYSIOLOGICAL ACTION. Hydrastine is not a narcotic, but exerts a paralytic and tetanizing effect, and causes an increase in blood pressure.

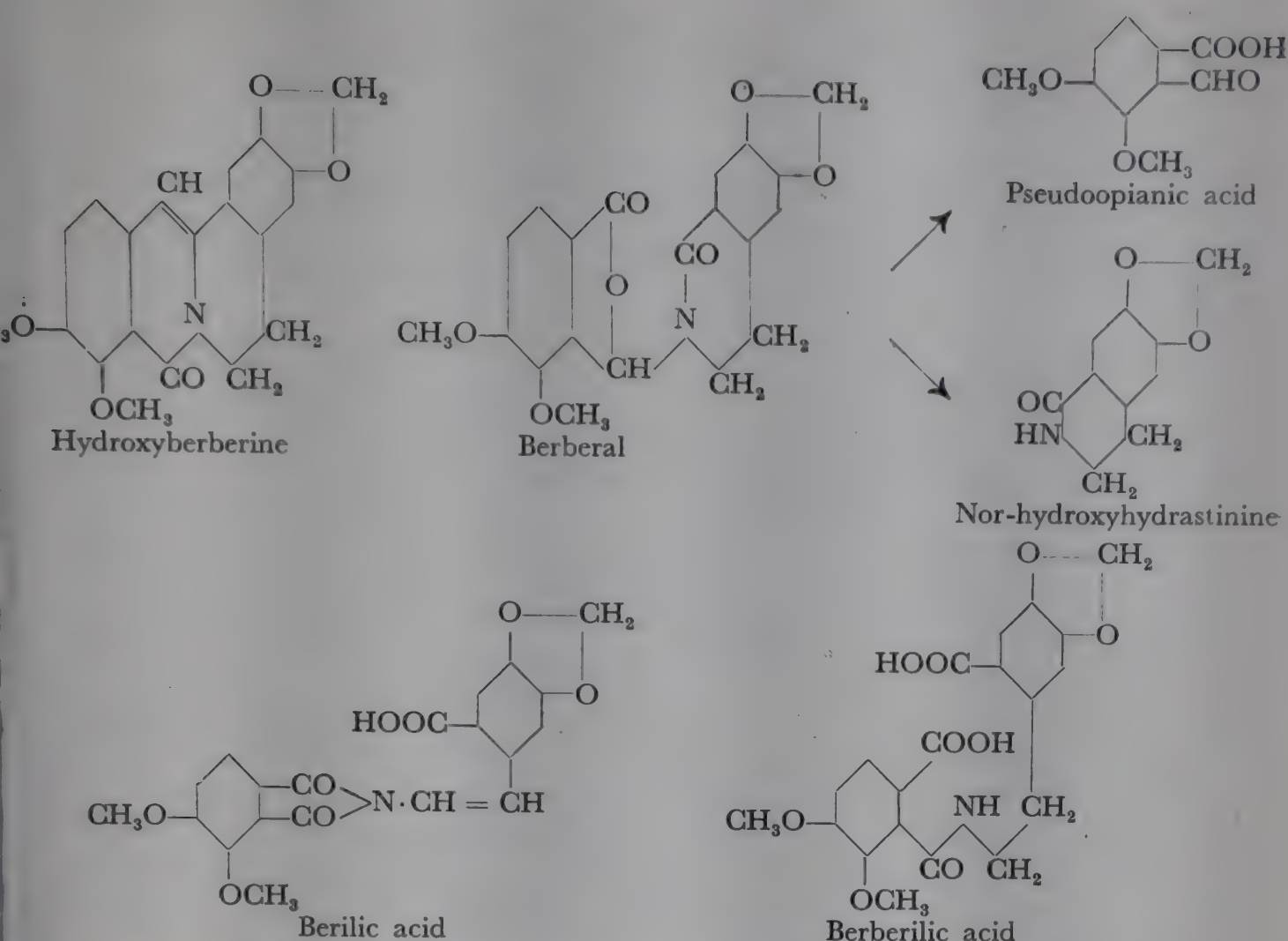
Hydrastinine contracts the blood-vessels, and therefore brings about an increase in blood pressure. It is used in gynæcology for similar purposes to ergot.

3. Berberine group

Berberine, $\text{C}_{20}\text{H}_{19}\text{NO}_5$. This yellow alkaloid is quite widely distributed in plants. It occurs, for example, in barberry root (*Berberis vulgaris*), in the root of *Hydrastis canadensis*, and in the bark of *Xanthoxylum clava Herculis*.

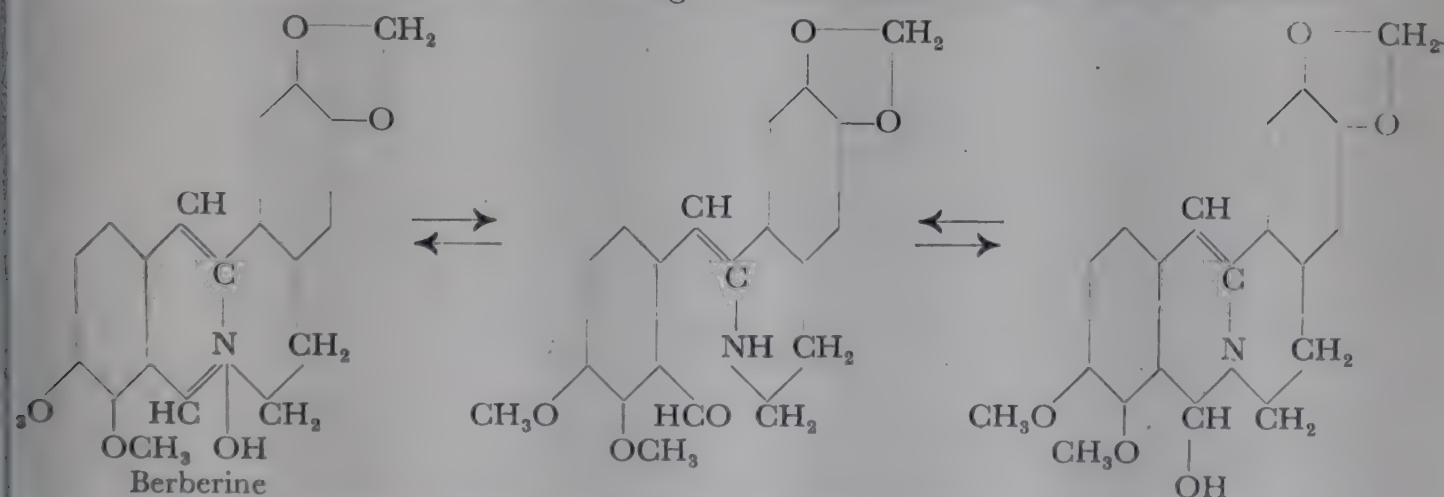
The determination of the constitution of berberine is based chiefly on the results of its oxidative degradation.

Controlled oxidation with potassium permanganate gives a series of oxidation products: *hydroxyberberine*, *berberal*, *berilic acid*, *berberilic acid*, of which the first two in particular have afforded an insight into the structure of the berberine molecule (Perkin, jun.). Berberal decomposes on boiling with dilute sulphuric acid to *pseudoopianic acid* (position isomeric of opianic acid), and *nor-hydroxyhydrastinine*. The latter can be converted by methylation into hydroxyhydrastinine (see above):



Berberal has been resynthesized from the two fission products, pseudoopianic acid, and nor-hydroxyhydrastinine (Perkin and Robinson).

From these reactions the following formula was derived for berberine itself



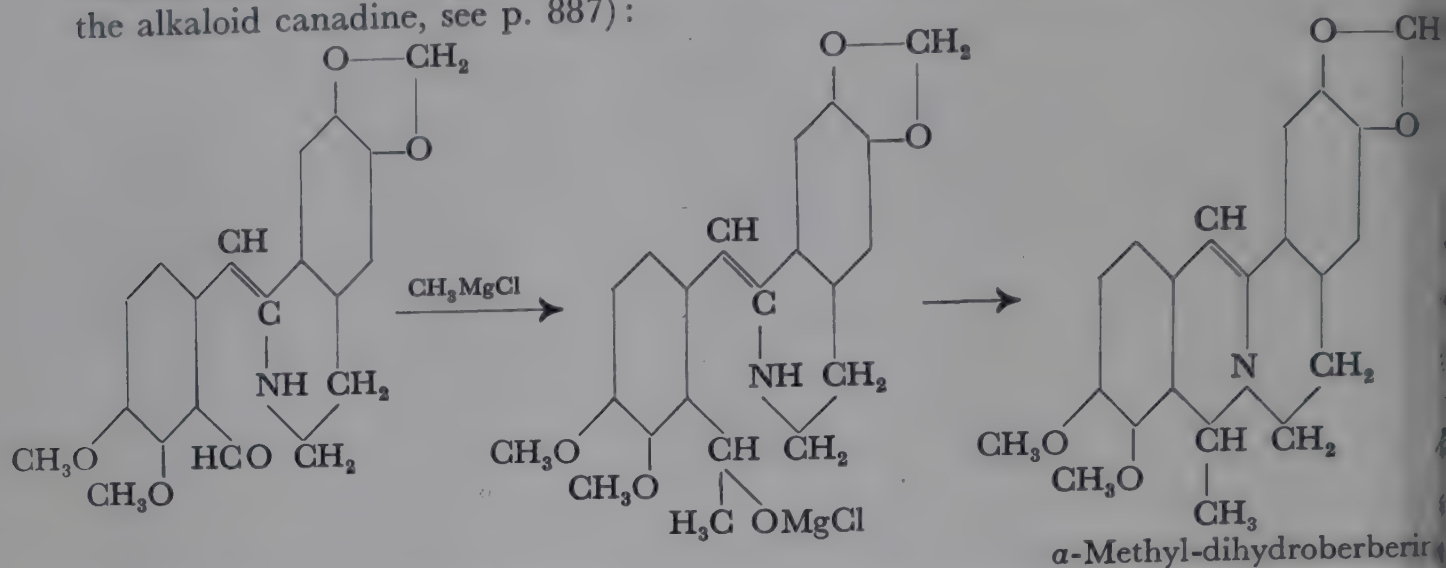
and this has been confirmed by all further investigations.

The vigorous oxidation of berberine with potassium permanganate in alkaline solution leads to hemipinic acid (see p. 887) and hydrastic acid (see p. 884). If nitric acid is used, berberonic acid, a pyridinetricarboxylic acid, is formed. These fission products leave no doubt as to the existence and nature of three of the ring systems of berberine.

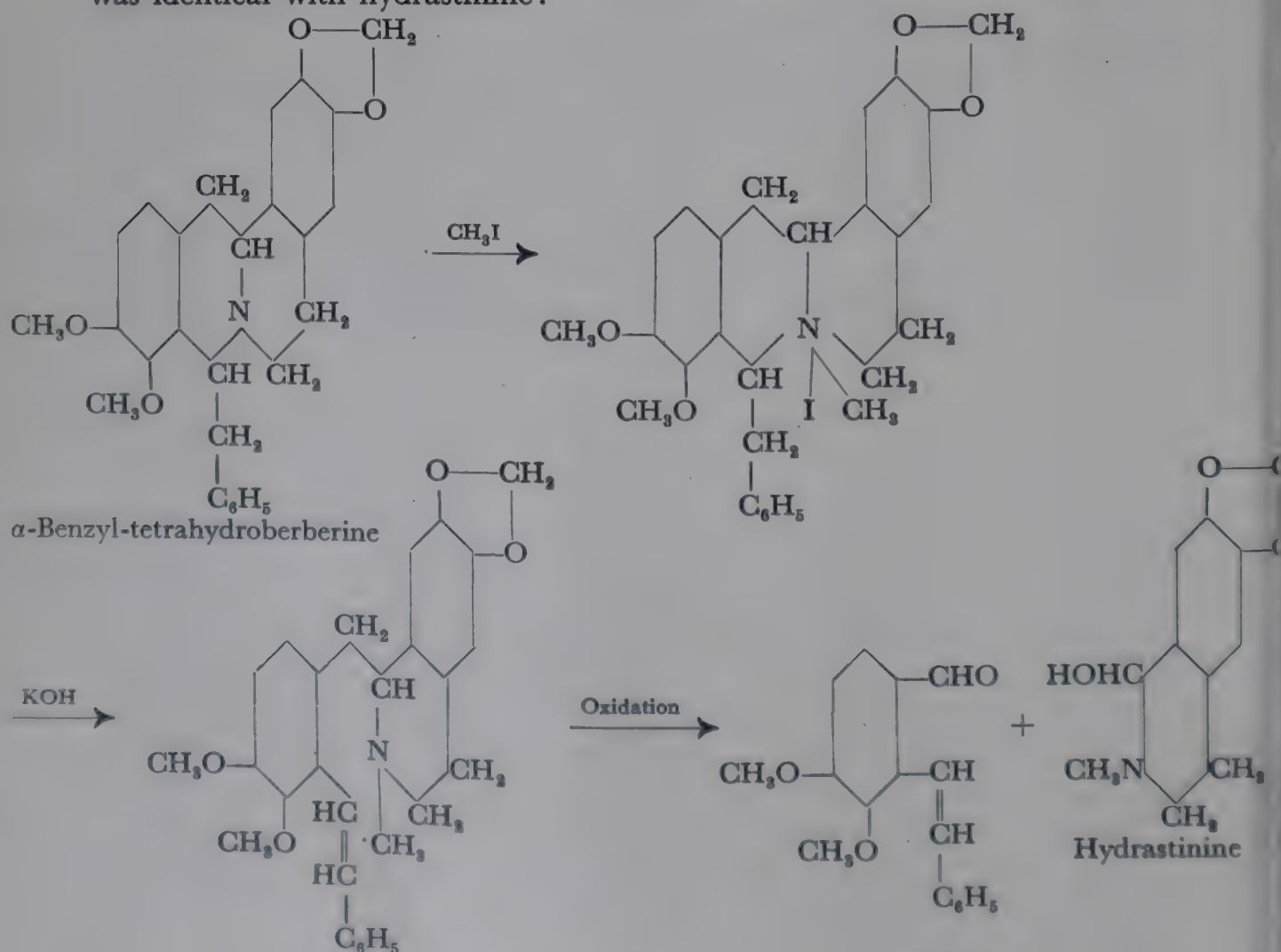
The above formulation of berberine indicates that the substance can act tautomerically, as a cyclic ammonium base, and as an aldehyde. In this respect it is completely in line with the behaviour of the structurally-related cotarnine

(see p. 880) and hydrastinine (see p. 883). As in the case of these two alkaloids, berberine forms salts with elimination of water.

Alkylmagnesium salts react with free berberine and also with its mineral acid salts giving *alkyl-dihydroberberines*. Oxidation of these gives homologous berberines, and reduction gives homologous tetrahydroberberines (homologues of the alkaloid canadine, see p. 887):



M. Freund has found hydrastinine to be readily accessible from the benzyl-dihydroberberine obtained from a benzylmagnesium salt and berberine. He reduced the compound to α -benzyl-tetrahydroberberine, prepared the methiodide of this, and boiled it with alkali. This resulted in rupture of the ring. The intermediate product was decomposed into two parts by oxidation, and one of these products was identical with hydrastinine:



Berberine is a weak, optically inactive base. It is appreciably soluble only in water and alcohol, and even so only on warming. Its salts are yellow. Physiologically it behaves similarly to hydrastine. It finds a limited use in cases of hæmorrhage as a stomachic and tonic.

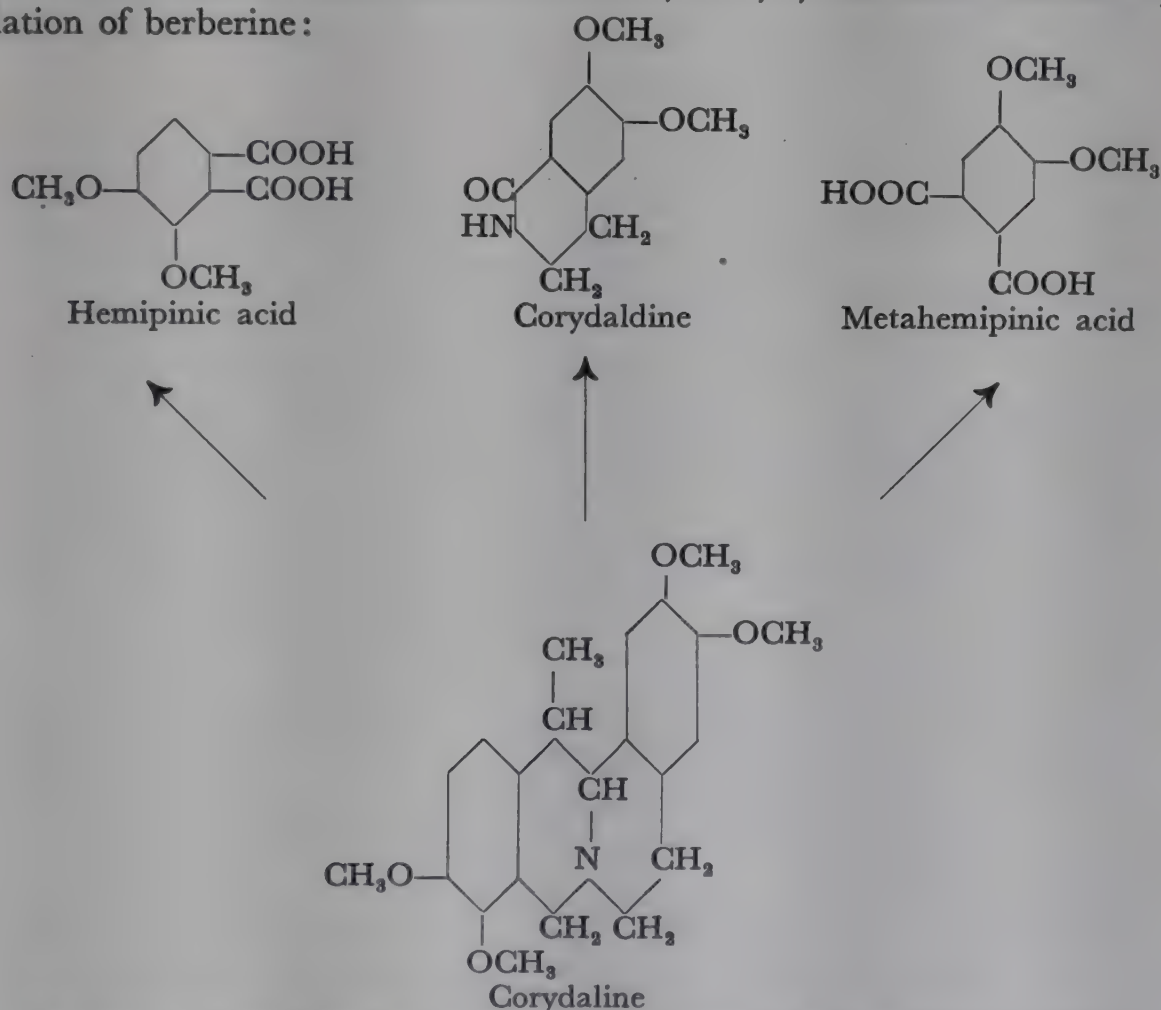
Canadine, $C_{30}H_{31}NO_4$. Canadine is the lævorotatory form of tetrahydroberberine. It can be prepared from berberine by reduction to the tetrahydro-compound, and resolving this base with bromocamphorsulphonic acid. Conversely it can be oxidized to berberine.

Under natural conditions it occurs together with hydrastine and berberine in the *Hydrastis* root and in the bark of a species of *Xanthoxylon*.

Corydaline, $C_{22}H_{27}NO_4$. A series of alkaloids occurs in *Corydalis cava* (hollow-root) and other species of *Corydalis*, which are similar in constitution to berberine, being isoquinoline derivatives and containing four ring systems in the molecule.

Mild oxidizing agents (e.g. iodine) dehydrogenate corydaline to *dehydro-corydaline*, $C_{22}H_{23}NO_4$, a base which also occurs naturally. The reaction corresponds to the formation of berberine from tetrahydroberberine.

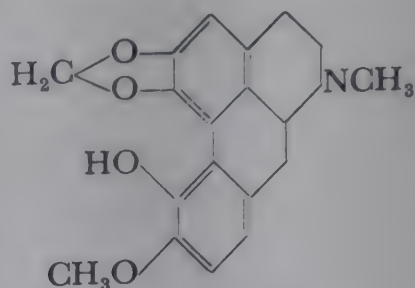
The products of its further oxidative degradation have been of particular importance in deciding the constitution of corydaline. The fission products obtained are hemipinic acid, metahemipinic acid, and a base *corydaldine*, $C_{11}H_{13}NO_3$, which resembles in its entire behaviour nor-hydroxyhydrastinine obtained by the oxidation of berberine:



Recently *dl*-corydaline has been prepared (Späth) from tetrahydro-methyl-papaverine by the Bischler-Decker-Pictet synthesis (by means of formaldehyde, see p. 816), although in very poor yield.

CORYBULBINE, $C_{21}H_{25}NO_4$, and *iso*CORYBULBINE, $C_{21}H_{25}NO_4$, two further alkaloids from hollow-root, only differ from corydaline in that they contain three methoxyl groups and one free phenolic hydroxyl group instead of four methoxyl groups. All three bases are demethylated by hydriodic acid to the same phenolic substance.

Another *Corydalis* alkaloid, *bulbocapnine*, is used in medicine against tremor symptoms, especially *paralysis agitans*.



CHAPTER 70. MORPHINE AND CRYPTOPINE ALKALOIDS. COLCHICINE¹

Opium, the concentrated juice of the seed capsules of various kinds of poppy (*Papaver somniferum*, etc.), which is used in exceedingly large quantities, especially in Asiatic countries, as a narcotic and a drug, contains a large number of alkaloids, of which about 25 have already been isolated. Some of them, such as papaverine, laudanosine, narcotine, etc., have already been dealt with in preceding chapters. Here, the *morphine alkaloids*, the most important opium bases, and the cryptopine alkaloids will be dealt with.

1. Morphine alkaloids

Morphine and Codeine. It appears best to deal with these two compounds together, since they are very closely related constitutionally, and the study of the one was also useful in connection with that of the other. Morphine was isolated from opium by Sertürner in 1806, and codeine by Robiquet in 1832, also from opium.

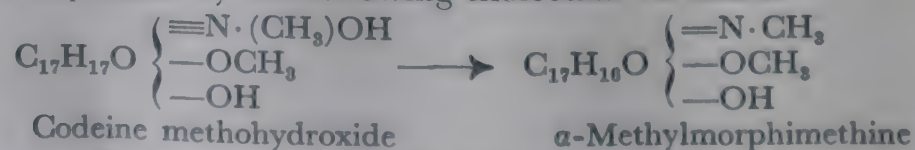
Morphine, $C_{17}H_{19}NO_3$, is a tertiary amine, which has a methyl group attached to the nitrogen. In addition, it possesses an alcoholic secondary hydroxyl group, and a phenolic hydroxyl. The latter makes it possible to dissolve the substance in alkalis.

Codeine, $C_{18}H_{21}NO_3$, is a monomethyl ether of morphine, the phenolic group being methylated. This follows, from the insolubility of codeine in alkalis, and also from its ability to give a ketone (codeinone, proof of the secondary nature of the alcohol group) when oxidized.

It is possible to obtain codeine from morphine by suitable methylation.

The nature of a considerable part of the carbon skeleton of these two alkaloids was arrived at by the distillation of morphine with zinc dust (Vongerichten and Schrötter). *Phenanthrene* is thus formed. Morphine and codeine are therefore derivatives of phenanthrene.

To determine the position of the oxygen atoms in codeine, the investigation of the product obtained by distilling codeine methohydroxide (Hofmann degradation) has been particularly valuable. It is called α -methylmorphimethine. Its formation from codeine is expressed by the following molecular formulæ:



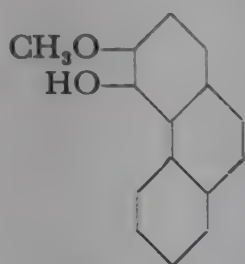
¹ L. F. SMALL and R. E. LUTZ, *Chemistry of the Opium Alkaloids*, (1932).

If α -methyldmorphimethine is heated with hydrochloric acid, it is split up into various fission products. The following *basic* degradation products are obtained:

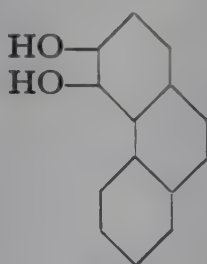


Both are probably secondary products from dimethyl-(β -chloroethyl)-amine, $\text{ClCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$, which is formed first.

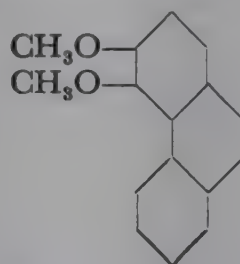
An *acid* decomposition product of α -methyldmorphimethine is *morphol monomethyl ether*; under other reaction conditions, *morphenol methyl ether*, a substance related to the former, is produced. Morphol monomethyl ether has proved to be identical with 3-methoxy-4-hydroxyphenanthrene. On demethylation it gives morphol (3:4-dihydroxyphenanthrene), and on methylation morphol dimethyl ether



Morphol mono-
methyl ether

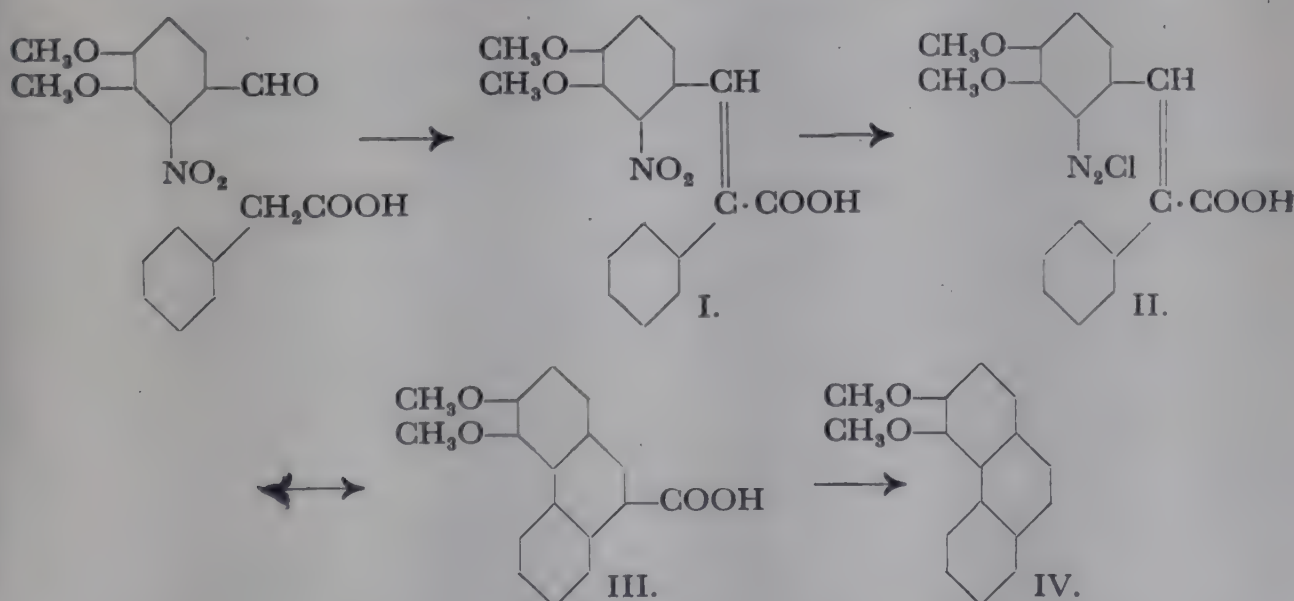


Morphol

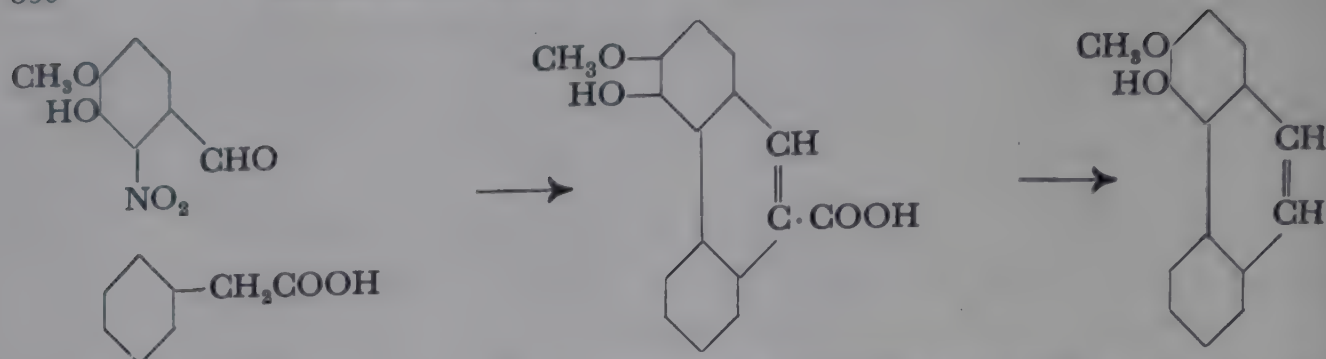


Morphol dimethyl ether

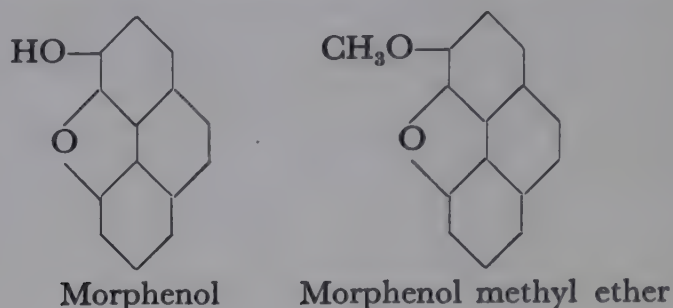
All these substances have been obtained synthetically, so that there is no doubt possible as to their constitution. Morphol dimethyl ether has been synthesized by Pschorr in the following way: 2-nitro-3:4-dimethoxybenzaldehyde is condensed with phenylacetic acid to 2-nitro-3:4-dimethoxy- α -phenylcinnamic acid (I), which is reduced to the corresponding amine, then diazotized (II), and the product treated with copper powder. Ring closure thus takes place to 3:4-dimethoxyphenanthrene-9-carboxylic acid (III). Morphol dimethyl ether (IV) is formed from the latter on heating, by elimination of carbon dioxide:



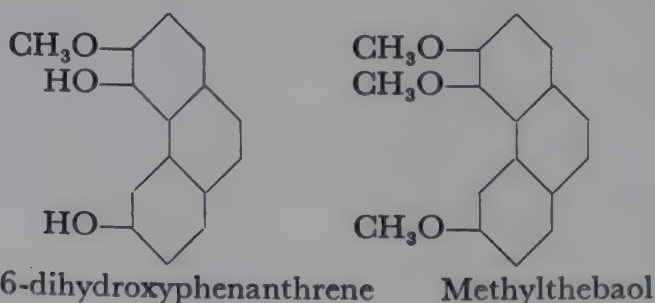
In essentially the same way morphol monomethyl ether, the actual fission product of codeine, has also been synthesized:



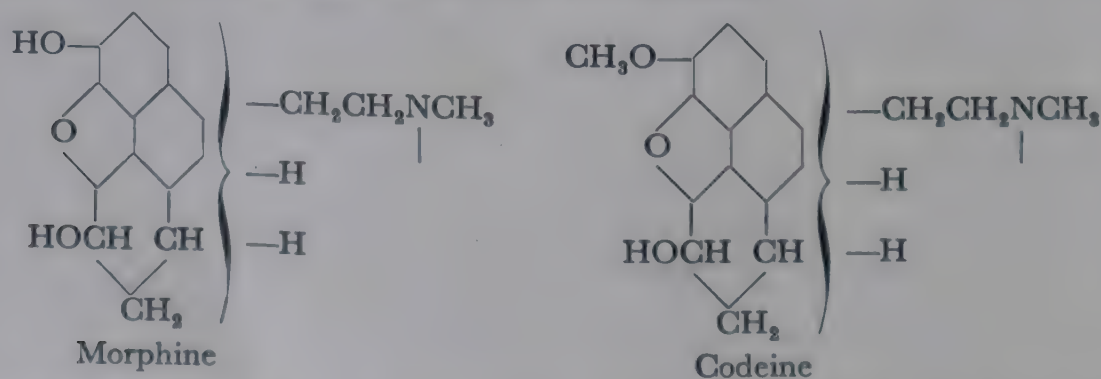
The investigation of the above-mentioned *morphenol* also gave a further important insight into the nature of the morphine oxygen atoms. This substance contains only one phenolic group, and one oxygen atom linked as in an ether. On reduction it yields morphol. Its structure must therefore correspond to the following formula:



Finally, the position of the secondary alcohol group in the morphine and codeine molecules is also known with certainty. Being a secondary alcohol, codeine is oxidized by chromic acid to a ketone, *codeinone*. On boiling with acetic anhydride for several hours this breaks down to N-methylaminoethanol, $\text{CH}_3\text{NH}\cdot\text{CH}_2\cdot\text{CH}_2\text{OH}$, and 3-methoxy-4:6-dihydroxyphenanthrene. The latter is produced as the diacetyl derivative. Its constitution has been verified by synthesis:



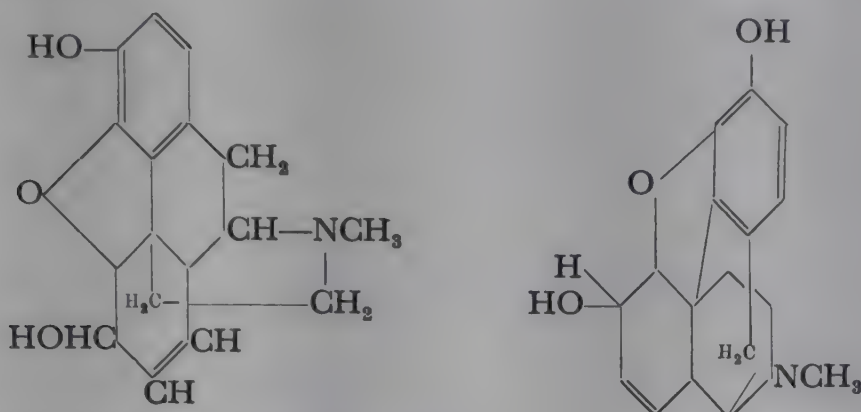
From these results of the degradation of morphine and codeine the following preliminary formulæ are derived for the two alkaloids:



The way in which the nitrogen-containing chain is linked with the phenanthrene skeleton has only recently been elucidated, in spite of numerous investig-

ations in this field. To give in detail the enormous amount of experimental evidence which has led to the various formulæ which have been proposed for morphine would exceed the scope of this textbook. Some results of the degradation of morphine, are moreover coupled with some uncertainty, since rearrangements take place very readily in the morphine molecule. This concerns especially the alcoholic hydroxyl which can easily move from position 6 to 8.

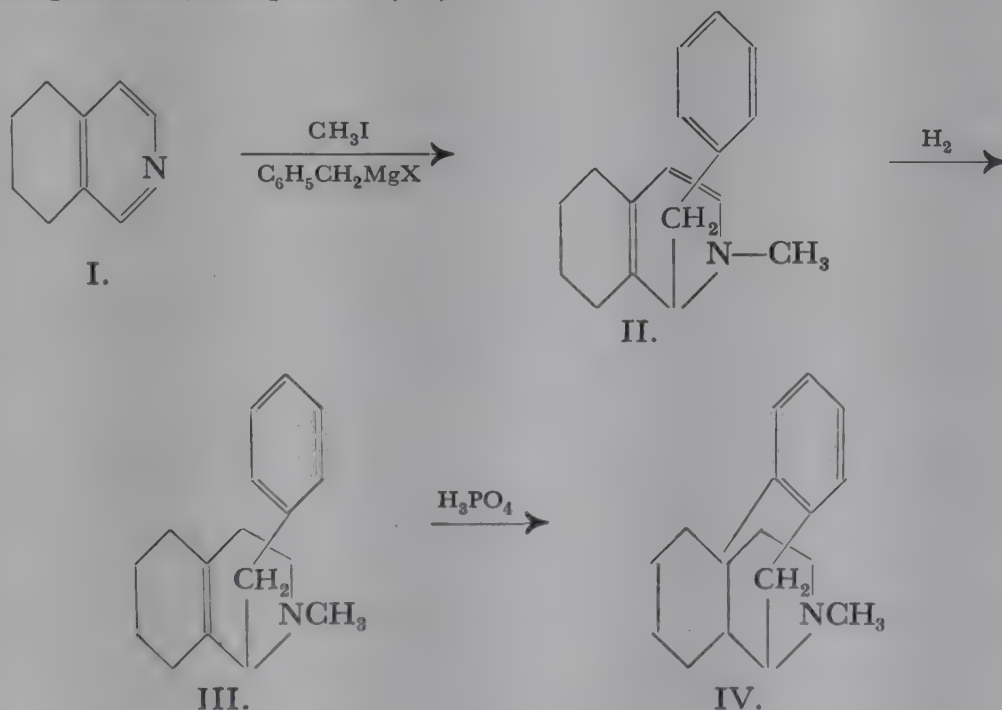
We shall only present the following formula for morphine (codeine) due to R. Robinson, which best accounts for all the known facts, and is also now generally accepted:



Robinson's formula for morphine (1925)

The alternative method of writing Robinson's formula, due to W. Awe, shows more clearly the connection between the compound and the *isoquinoline* alkaloids.

"N-methylmorphinan", the parent compound of the morphine series, has been synthesized by Grewe in a very interesting and relatively simple way. The starting material 5:6:7:8-tetrahydro*isoquinoline* (I) is first treated with CH_3I to give the methiodide, and the latter with a benzylmagnesium salt affords N-methyl-1-benzyl-1:2:5:6:7:8-hexahydro*isoquinoline* (II). Partial reduction of II leads to N-methyl-1-benzyl-1:2:3:4:5:6:7:8-octahydro*isoquinoline* (III). On heating this with 65% phosphoric acid, intramolecular addition of the benzene ring to the double bond of the *isoquinoline* nucleus takes place, thus yielding N-methylmorphinan (IV):



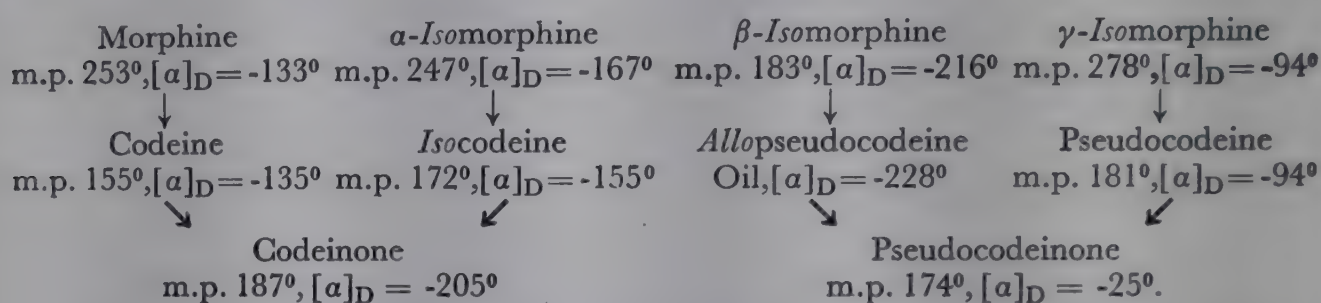
N-methylmorphinan, like morphine, has strong analgesic properties.

Several isomerides of both morphine and codeine are known. The isomerides

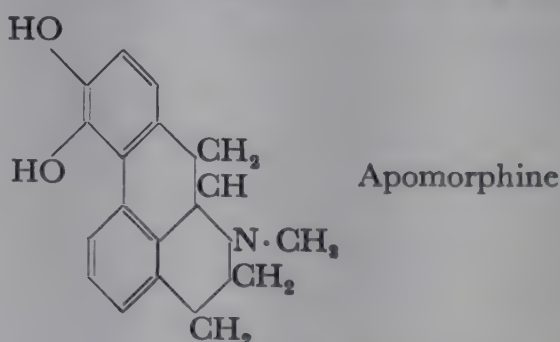
of morphine are called α -isomorphine, β -isomorphine, γ -isomorphine; those of codeine are called isocodeine, allopseudocodeine, and pseudocodeine.

Morphine and α -isomorphine are stereoisomerides. They differ in the spatial configuration of the H and OH at the carbon atom bearing the alcohol group. By methylation, morphine is converted into codeine, and α -isomorphine into isocodeine. There is therefore the same stereochemical relationship between codeine and isocodeine as between morphine and α -isomorphine, and the same codeinone is obtained from both of them by oxidation.

β -Isomorphine and γ -isomorphine are a similar stereoisomeric pair. However, they contain the alcoholic hydroxyl group probably at the eighth and not at the sixth carbon atom of the phenanthrene skeleton. On methylation, they yield allopseudocodeine and pseudocodeine, respectively. If the latter two codeine isomerides are oxidized, a ketone, pseudocodeinone, is formed which is different from codeinone:



Morphine undergoes important structural changes when treated with dehydrating agents, e.g. on heating with hydrochloric acid or sulphuric acid. The reaction product is *apomorphine*. It no longer contains the original carbon skeleton of morphine, and can be regarded both as a phenanthrene and as an *isoquinoline* derivative:



PHYSIOLOGICAL ACTION. In human beings *morphine* acts principally on the central nervous system. It is a sedative, and in large doses a narcotic. The activity of the sensitive peripheral nerves is inhibited. It is therefore of great practical use in relieving pain.

By repeated use the system quickly becomes accustomed to the poison, and the organism then tolerates large doses. If the body remains under the continued action of morphine, considerable injury (emaciation, weakness, imbecility) results. Since the effect of morphine is a pleasant state for many people, the danger of becoming addicted to the drug is great (morphinism). Smoking opium produces the same effects.

Another important property of morphine is its effect on the peristalsis of the intestine. It depresses its movement. Hence the value of morphine in cases of diarrhoea and other disorders of the bowels.

Codeine lacks the narcotic action of morphine almost completely, but shows a stronger tetanizing action than the latter. It is used in medicine in the treatment of coughs. *Dionin*, morphine ethyl ether, and *paracodin*, dihydrocodeine, are also used in medicine for the same purpose.

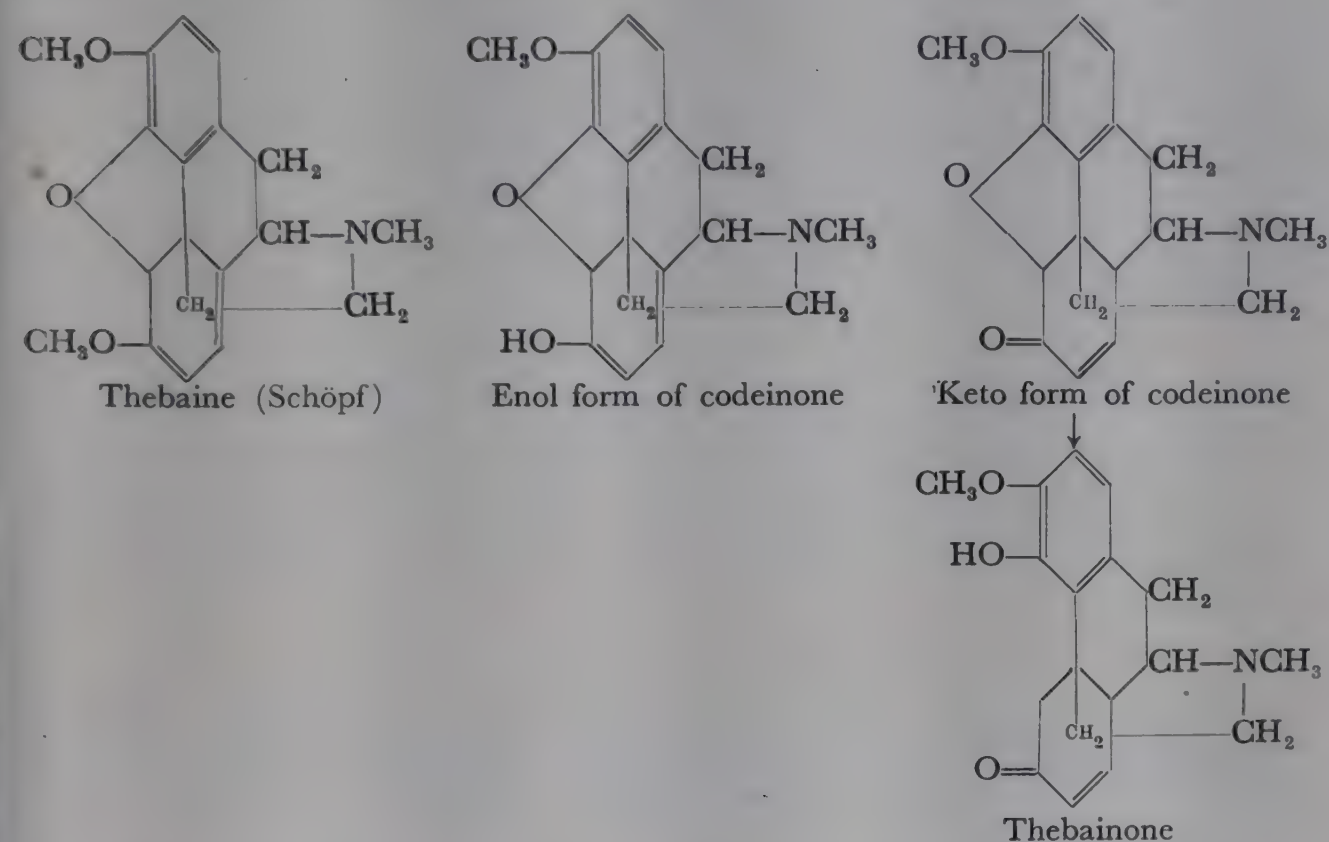
Apomorphine has a strong stimulating action on the central nervous system. It is one

of the most powerful emetics. This property particularly is made use of in medicine. In small doses it is used as an expectorant.

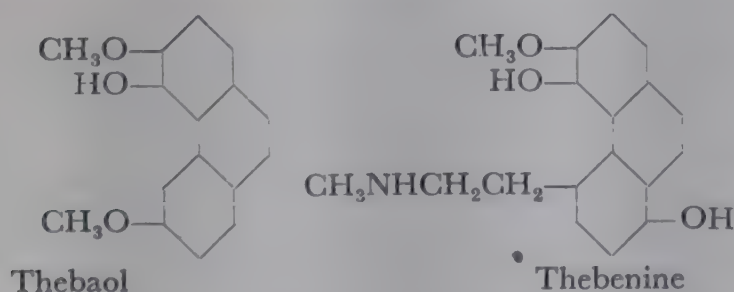
Thebaine, $C_{19}H_{21}NO_3$. Thebaine is found in opium, but only in small quantities, and was discovered in it in 1835 by Pelletier.

It is very simply related to morphine, and especially to codeine. If it is hydrolysed with dilute sulphuric acid it breaks down into methyl alcohol and codeinone. It is therefore the methyl ether of the enol form of codeinone.

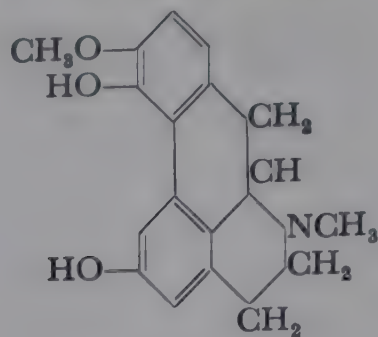
By reduction of codeinone with stannous chloride, its oxygen bridge is broken, and thebainone is formed:



Different cleavage processes lead to characteristic degradation products from thebaine. Acetic anhydride decomposes the alkaloid on heating into *hydroxyethyl-methylamine* and *thebaol*, 3:6-dimethoxy-4-hydroxyphenanthrene. By dilute hydrochloric acid, on the other hand, it is converted into a derivative of 3:4:8-trihydroxyphenanthrene, *thebenine*. The last reaction is accompanied by the appearance in position 8 of the hydroxyl group from position 6, and emphasizes again the great tendency for intramolecular rearrangements in the group of the morphine bases:



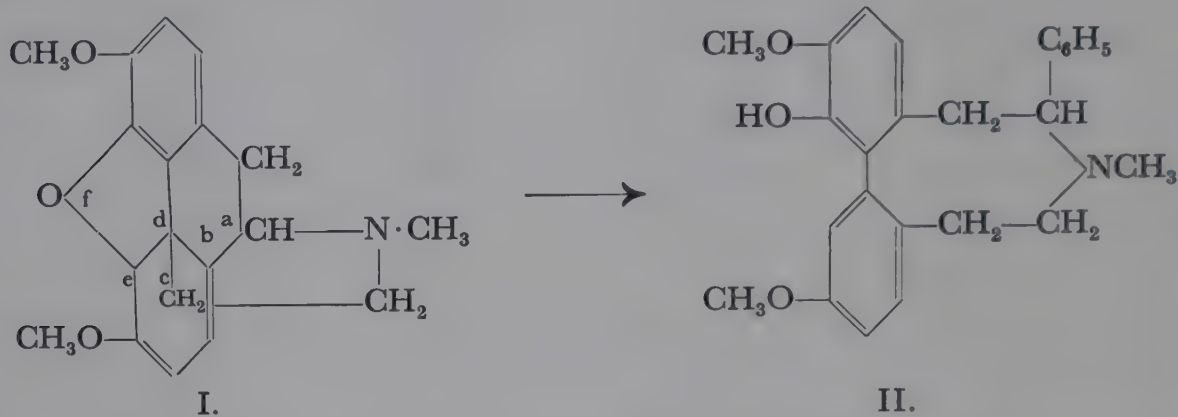
On heating with concentrated hydrochloric acid thebaine behaves in a similar manner to morphine. *Morphothebaine*, a derivative of apomorphine, is formed:



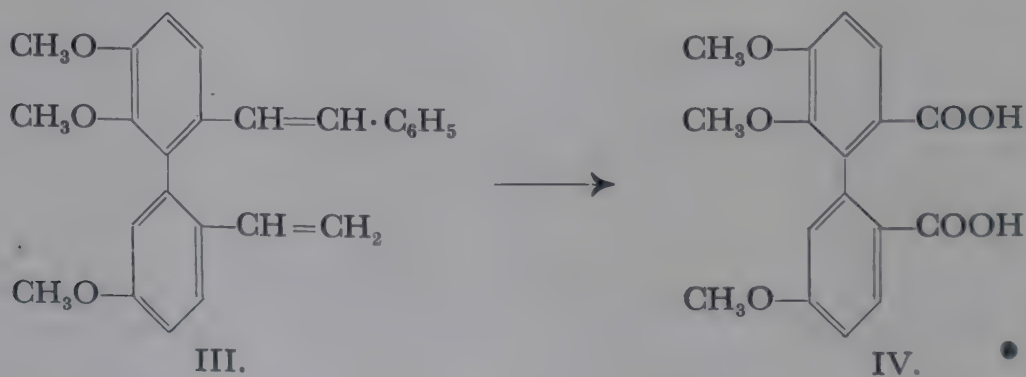
Morphothebaine

Thebaine melts at 193° , $[\alpha]_D = -218^{\circ}$. It is a powerful poison causing convulsions. Of all the opium alkaloids it is the most toxic. It has hardly any narcotic action. It is not used in medicine.

An interesting and peculiar rearrangement in the thebaine molecule (I) results from the action of a phenylmagnesium salt, phenyldihydrothebaine thus being formed (M. Freund). Its structure as given in formula II has been elucidated by R. Robinson.



Structure II for the phenyldihydrothebaine is proved, since on exhaustive methylation the compound is degraded to the biphenyl derivative III, which, in turn, on oxidation yields 6:5:5'-trimethoxybiphenyl-2:2'-dicarboxylic acid (IV):



The rearrangement may be imagined to proceed in the following manner: The attacking phenyl anion brings an electron pair to the carbon atom (a) of thebaine (I); then the carbon atom (c) of the ethanamine chain is linked to the carbon atom (b) by means of the electrons of the bond (a,b). The electrons of the bond (c,d) migrate to (d,e) thus causing the six-ring to become aromatic. The electrons of the bond (e,f) are taken up by the oxygen, and the latter thus receives a negative charge, which is compensated by the taking up of a proton when the organometallic compound is decomposed with water.

The biphenyl derivative (III) has proved to be optically active; this has to be ascribed to the non-coplanar arrangement of the two phenyl nuclei. This case thus provides an example of an optically active biphenyl derivative which has been formed from a naturally occurring compound (cf. p. 395).

2. Colchicine, $C_{22}H_{23}NO_6$.

COLCHICINE, the alkaloid of meadow saffron (*Colchicum autumnale*), was discovered in this plant by Pelletier and Caventou in 1819, and was recognized later by Geiger and Hesse as a new type of base. Windaus and, more recently, Cook have attempted to elucidate the structure of colchicine. The formula of this alkaloid, however, is not yet known with certainty.

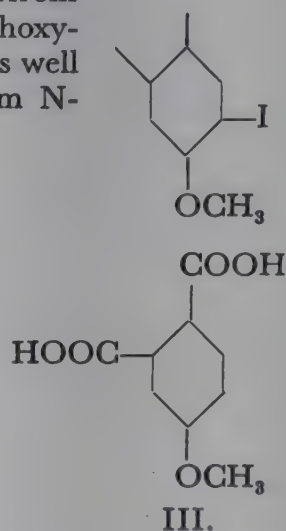
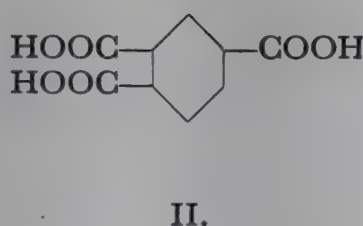
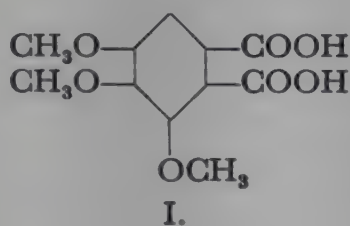
9-Methylphenanthrene was obtained by distillation of a colchicine derivative, and for this reason it was thought that colchicine was derived from phenanthrene. Recent investigations, however, have thrown doubt on this conclusion.

Dilute mineral acids decompose colchicine exceedingly readily into methyl alcohol and *colchiceine*, $C_{21}H_{23}NO_6$, which Windaus regarded as an aldehyde-enol, on the grounds that the $>C=CHOCH_3$ grouping changes into $>C=CHOH$, when acted upon in this way.

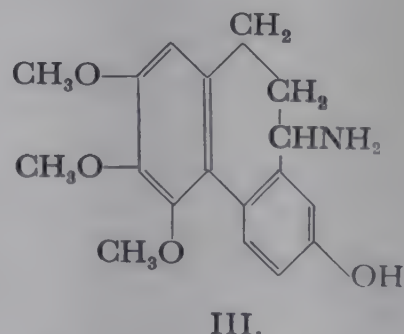
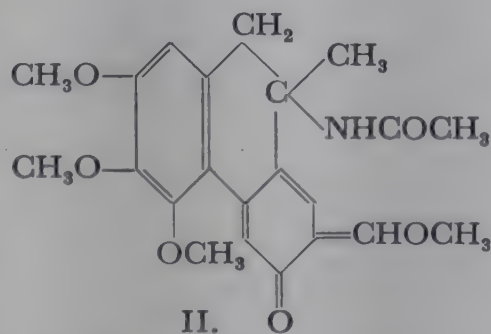
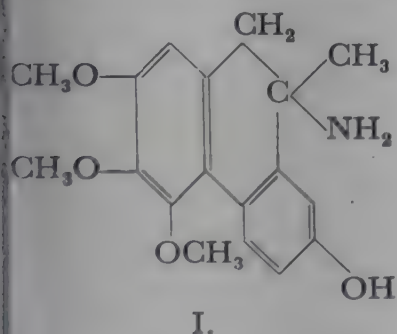
Treatment with stronger acids removes from the colchicine molecule also an acetyl radical attached to nitrogen. A primary amine, "trimethylcolchicinic acid" is thus formed:



Information concerning the carbon rings of the alkaloid is obtained from its degradation. By various oxidative fission reactions 3:4:5-trimethoxy-1:2-phthalic acid (I), trimellitic acid (II) (and terephthalic acid), as well as 4-methoxyphthalic acid (III) have been isolated, the latter from N-acetyl-iodocolchinol methyl ether with the grouping alongside

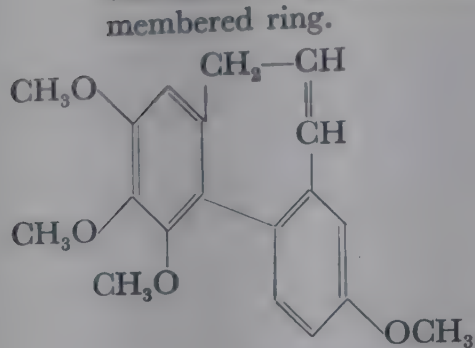


When colchiceine is treated with sodium hypoiodite, "N-acetyl-iodocolchinol", $C_{20}H_{22}O_5NI$, is formed, which is converted by reduction into N-acetyl-colchinol, $C_{20}H_{23}O_5N$. The latter gives colchinol, $C_{18}H_{21}O_4N$, by means of alcoholic hydrochloric acid. Windaus attributed structure I to this substance, and his formula for colchicine (II), which is based on the different degradation reactions mentioned above, accordingly contains three six-membered carbon rings.

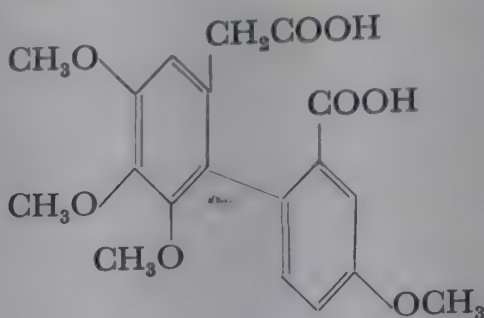


According to recent work by Cook, however, the second ring should be seven-membered, and colchinol would have structure III. Deaminocolchinol methyl ether (IV) on oxidation affords an acid (V) which by ester condensation is converted into a phenanthrene

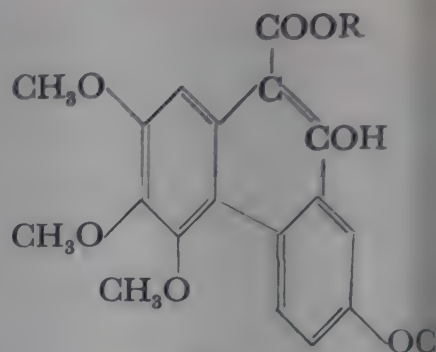
derivative (VI). Colchicine itself must therefore have a new formula containing a seven-membered ring.



IV.



V.



VI.

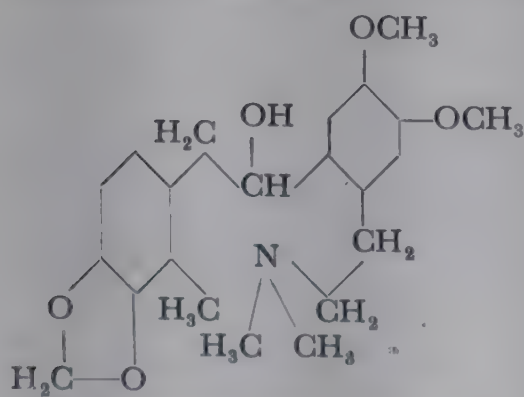
Colchicine is amorphous, and dissolves in cold water; it reacts neutral and is very poisonous. On account of its alleged value in the treatment of gout it is occasionally used in medicine.

3. Alkaloids of the cryptopine type

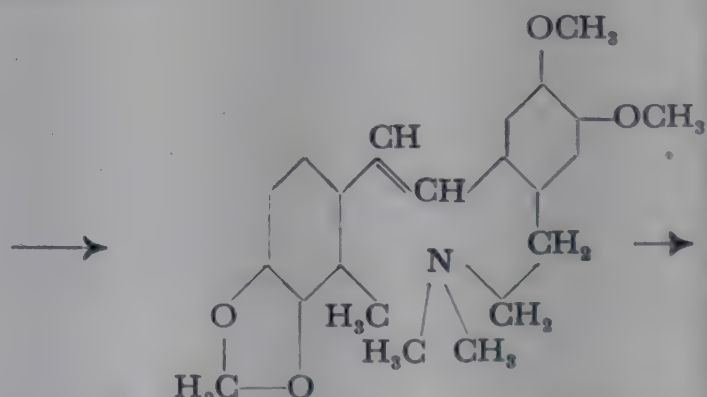
It has recently been recognized that in the opium alkaloids *cryptopine* and *protopine* a new type of heterocyclic ring-system occurs, consisting of ten ring members, which also appears to exist in some *chelidonium* alkaloids (from *Chelidonium majus*), e.g. in β -homochelidonine. As will be seen from the following, these bases are related to the berberine alkaloids in constitution.

Cryptopine, $C_{21}H_{23}NO_5$. The formula given below for this alkaloid, due to Perkin jr., is based on the following facts:

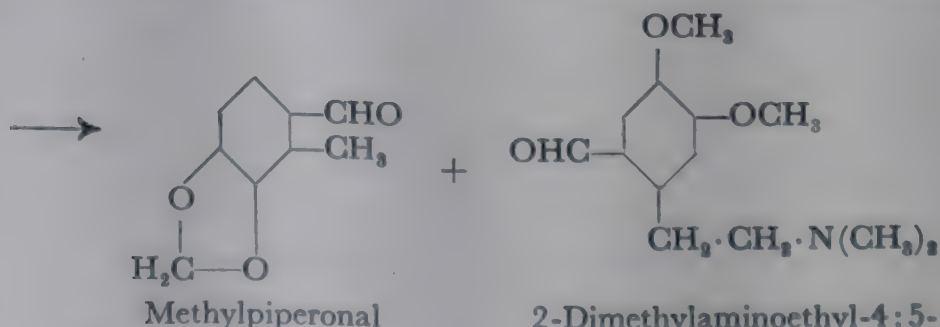
The addition product of dimethyl sulphate and cryptopine can be reduced to methyltetrahydrocryptopine (I). By the action of acetyl chloride this loses one molecule of water, and forms anhydro-methyltetrahydrocryptopine (II). The formula proposed for this compound is supported by the fact that by gentle oxidation the substance breaks down into 2-(β -dimethylaminoethyl)-4:5-dimethoxybenzaldehyde and methylpiperonal:



I. Methyltetrahydrocryptopine




II. Anhydro-methyltetrahydrocryptopine



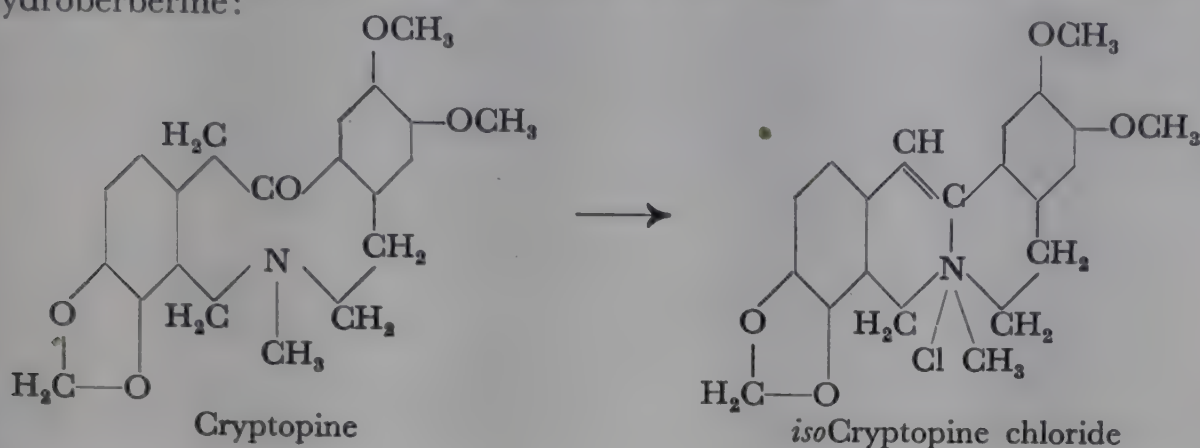
Methylpiperonal

2-Dimethylaminoethyl-4:5-dimethoxybenzaldehyde

Another degradation product resulting from the oxidation of cryptopine is

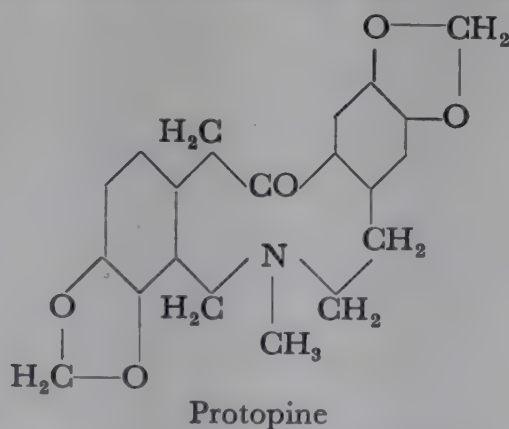
metahemipinic acid, , the formation of which is also in agreement with the formula for cryptopine given below.

Special importance attaches to the connection between cryptopine and the berberine bases. When treated with hydrochloric acid cryptopine readily undergoes intramolecular ring closure with elimination of water. *iso*Cryptopine chloride is thus formed, which can be regarded as most closely related to berberine or dihydroberberine:



Cryptopine is found in opium. It melts at 218–219°. It is optically inactive. It produces convulsions in warm-blooded animals.

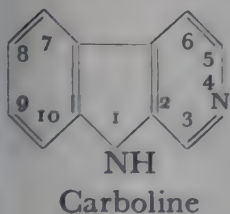
Protopine, $C_{20}H_{19}NO_5$. This base belongs to the same type as cryptopine, but has instead of the two methoxy-groups, a methylenedioxy grouping:



It occurs in numerous species of *Papaveraceae*. It melts at 208°.

CHAPTER 71

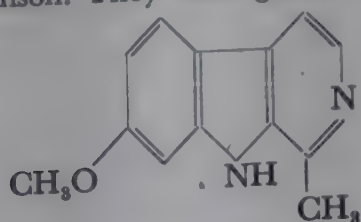
CARBOLINE ALKALOIDS. VASICINE (PEGANINE)



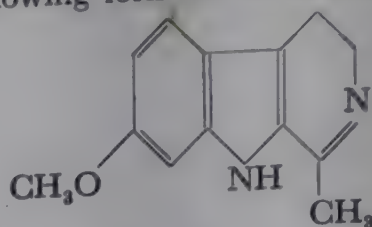
The carboline ring system consists of an indole nucleus condensed with a pyridine ring. Several alkaloids are derived from this, being partly simple derivatives of carboline (harmine, harmaline, harman), and partly containing further ring systems in their molecules (e.g. yohimbine, evodiamine, rutæcarpine).

Harmine alkaloids. The harmine bases are fairly abundant in plants. Thus, harmine is found, for example, in *Peganum harmala*, in an American liana (Yaje), and in *Banisteria Caapi*. Harmaline is found in *Peganum harmala*. Harman occurs in *Arariba rubra*, *Symplocos racemosa*, etc.

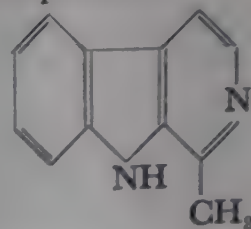
The investigation of the constitution of these alkaloids is due chiefly to Perkin and Robinson. They have given the following formulæ for the three compounds:



Harmine, m.p. 264–265°

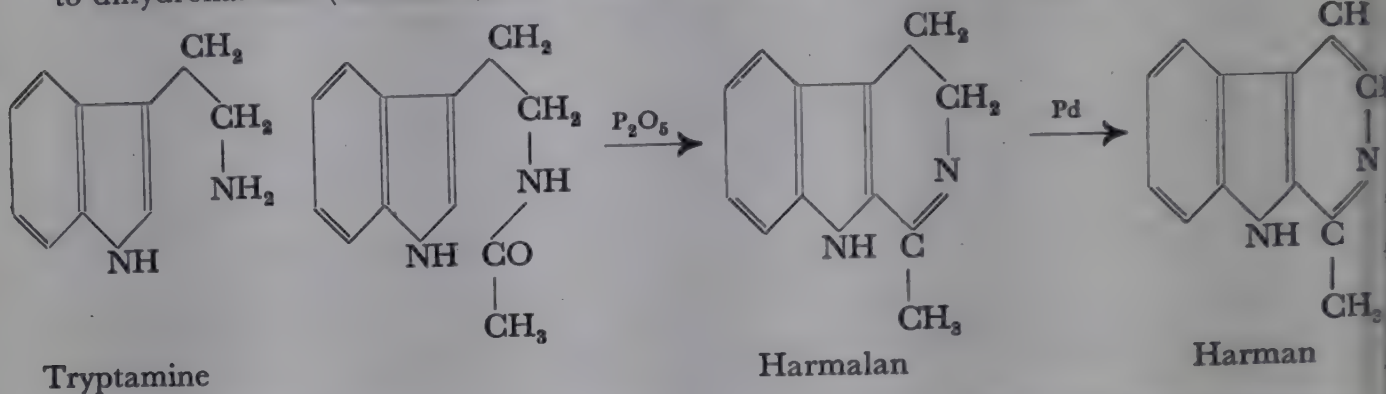


Harmaline, m.p. 251°
(Dihydroharmine)



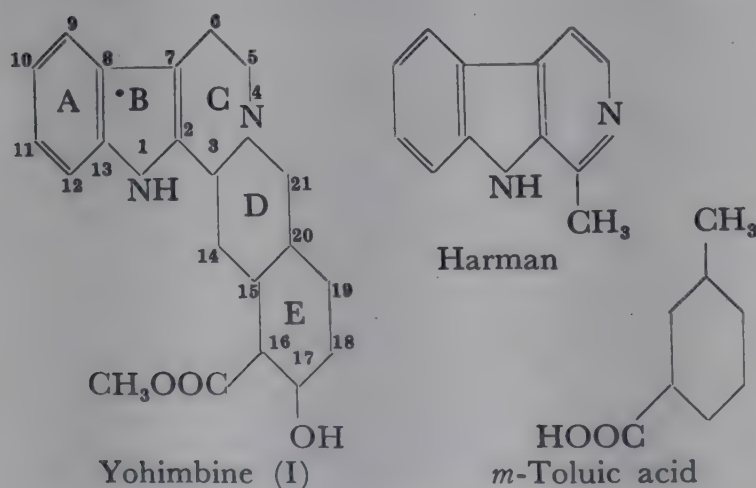
Harman, m.p. 237°

These have been proved by various syntheses, which are, in part, carried out in a similar way to the well-known *isoquinoline* synthesis of Napieralsky, Pictet, and Decker. Thus, for the preparation of harman, the starting product is, for instance, 3-[β -aminoethyl]-indole (tryptamine). This is acetylated and anhydridized by phosphorus pentoxide to dihydroharman (harmalan), and finally the latter is dehydrogenated:



In an analogous way harmaline and harmine have been obtained from methoxytryptamine.

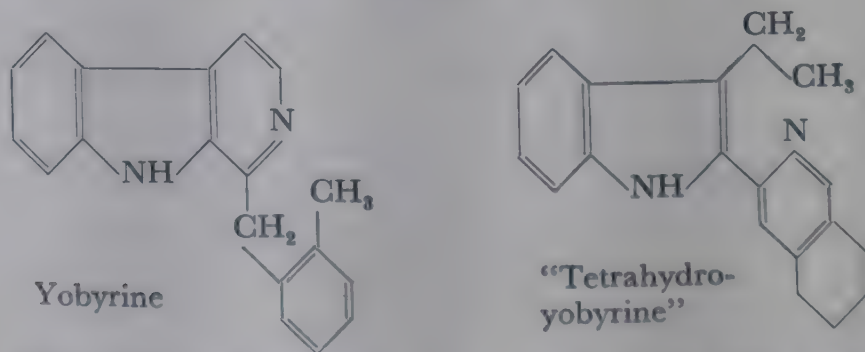
Harmine finds a limited use in medicine (Parkinson's disease).



Yohimbine (I), $C_{20}H_{16}ON_2$, and "tetrahydroyobyryne", $C_{19}H_{20}N_2$.

Yohimbine, $C_{21}H_{26}N_2O_3$, is found in the leaves and bark of *Corynanthe Yohimbe*, the yohimbe tree. It dilates the blood vessels and is used, especially in veterinary medicine, as an aphrodisiac.

Recent investigations by Wibaut, and especially Barger, Scholz, and Hahn, have provided some insight into the constitution of this alkaloid. It can be dehydrogenated with selenium, well-characterized degradation products being formed: yobyryne, $C_{19}H_{16}N_2$, ketoyobyryne,

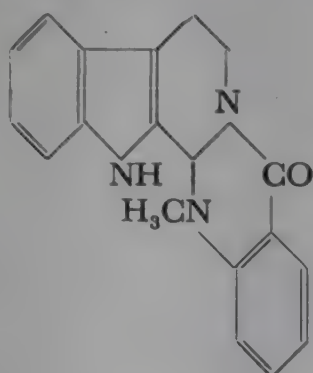


Further degradation of these products, or of yohimbine itself (fusion with alkali oxidation), gives rise to smaller fission products, viz. 2:3-dimethylbenzoic acid, hemimellitic acid, *m*-toluic acid, berberonic acid (1:3:4-pyridinetricarboxylic acid), and harman. Distillation

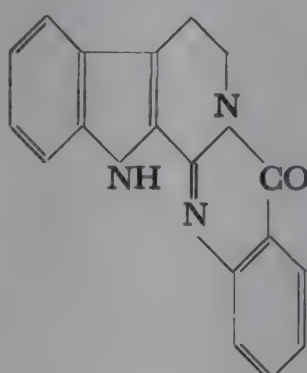
with zinc dust gave harman and *p*-cresol. On the basis of these degradation products, formula (I) was arrived at. The compound contains a CH_3OOC -group at C-atom 16, further an alcoholic OH-group in ring E, at C-atom 17. On dehydrogenation with aluminium phenate, the carboxyl group is eliminated and the ketone yohimbone is produced.

Evodiamine. Rutæcarpine. These two plant bases, investigated by Asahina and Ohta, occur in the fruit of *Evodia rutæcarpa*. They also contain the carboline ring system in their molecules. They differ from the above-mentioned alkaloids, however, in possessing a further nitrogen-containing ring.

EVODIAMINE, $\text{C}_{19}\text{H}_{17}\text{ON}_3$, has the constitution (I), RUTÆCARPINE, $\text{C}_{18}\text{H}_{13}\text{ON}_3$, corresponds to formula II:

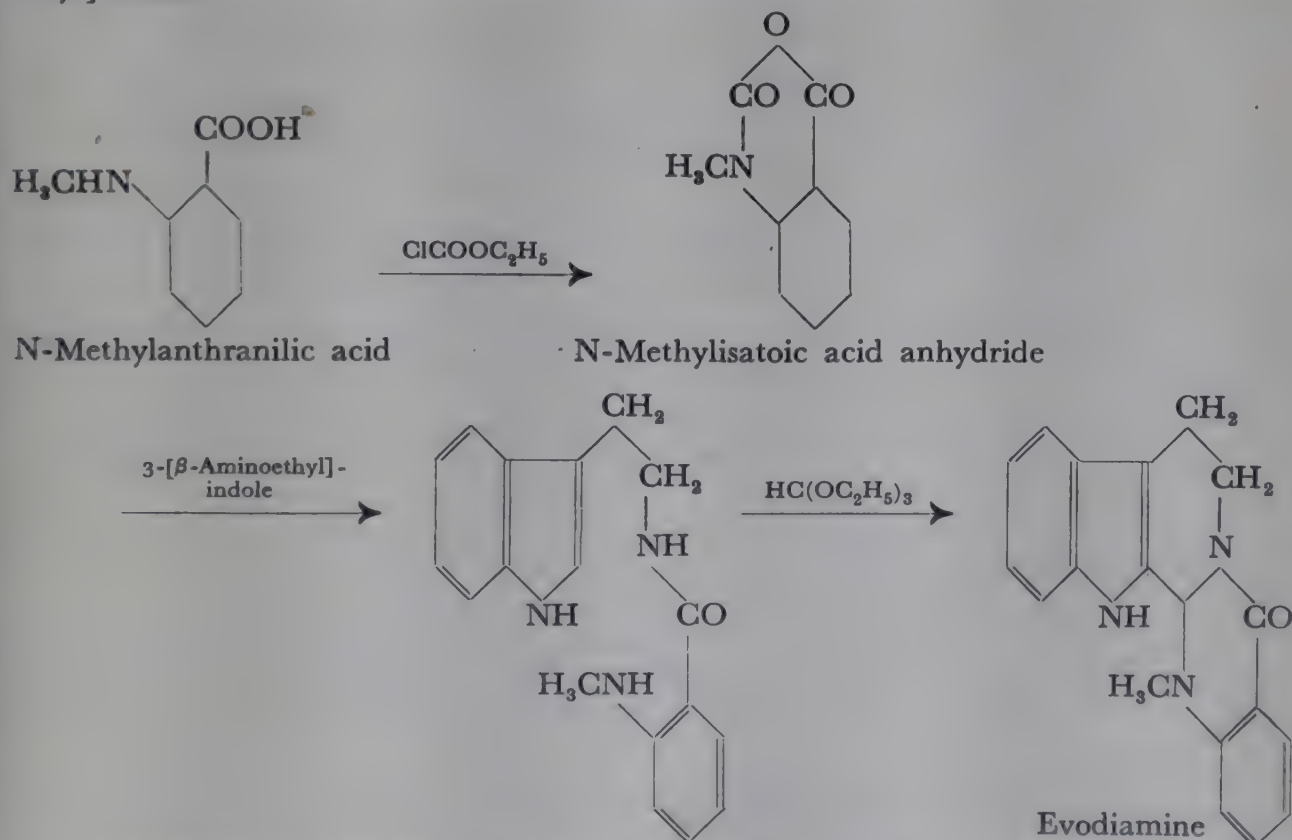


I (m.p. 278°)

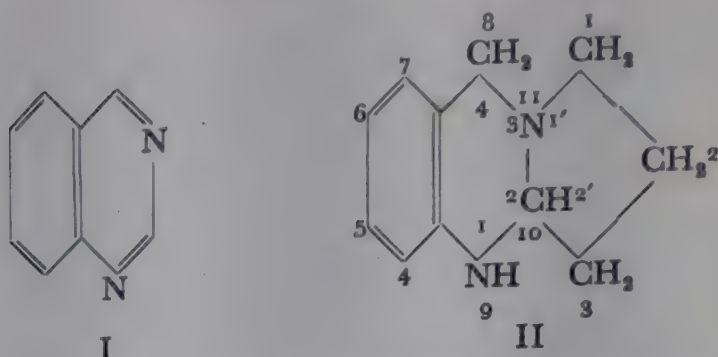


II (m.p. 258°)

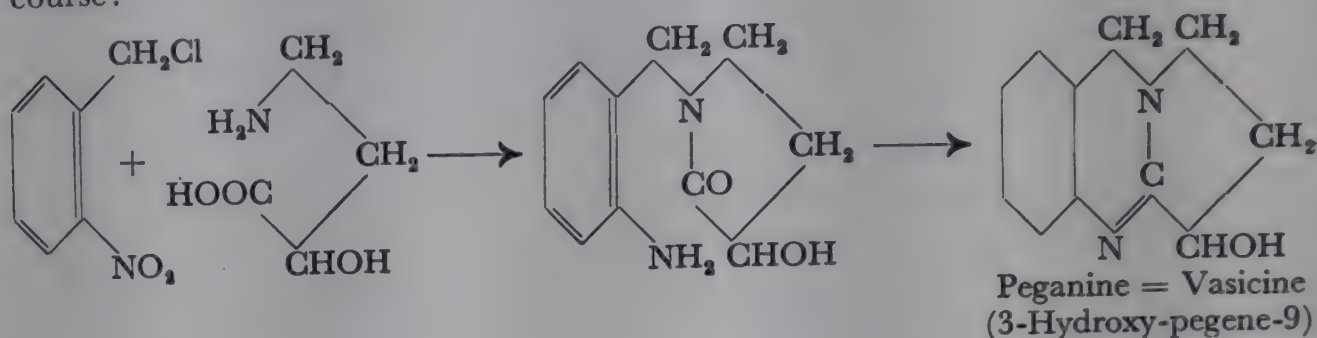
On heating dry evodiamine it is converted into rutæcarpine with evolution of methane. Racemic evodiamine has been synthesized from N-methylantranilic acid and 3-[β -aminoethyl]-indole:



Vasicine (peganine). The alkaloid vasicine from *Adhatoda vasica* (Nees) is identical with peganine from *Peganum harmala*. At present both names are used in the literature. Vasicine is a derivative of quinazoline (I), a heterocyclic parent substance, which up to now has not often been met with in nature. The tricyclic ring system II, from which vasicine is derived, is called pegan (pyrrolidino-1':2'; 3:2-quinazoline tetrahydride-1:2:3:4).



The constitution of peganine is established by synthesis. Using α -hydroxy- γ -aminobutyric acid and *o*-nitrobenzyl chloride, the synthesis takes the following course:



CHAPTER 72

ALKALOIDS OF ERGOT, PILOCARPINE, ESERINE, CYTISINE, SOLANINE, STRYCHNINE, AND ALKALOIDS OF UNKNOWN CONSTITUTION

Alkaloids of ergot. Extracts of ergot, a fungus (*Claviceps purpurea*) growing on grain, particularly rye, have been used in medicine for various purposes for centuries. They contain a series of interesting alkaloids, which are responsible for the strong physiological actions, in particular, causing strong contraction of the uterus.

The alkaloids that have been isolated from ergot up to the present are:

1. Ergotamine group

Ergotamine	$C_{33}H_{35}O_5N_5$
Ergotaminine	$C_{33}H_{35}O_5N_5$
Ergosine	$C_{30}H_{37}O_5N_5$
Ergosinine	$C_{30}H_{37}O_5N_5$

2. Ergotoxine group

Ergocristine	$C_{35}H_{39}O_5N_5$
Ergocristinine	$C_{35}H_{39}O_5N_5$
Ergocryptine	$C_{32}H_{41}O_5N_5$
Ergocryptinine	$C_{32}H_{41}O_5N_5$
Ergocornine	$C_{31}H_{39}O_5N_5$
Ergocorninine	$C_{31}H_{39}O_5N_5$

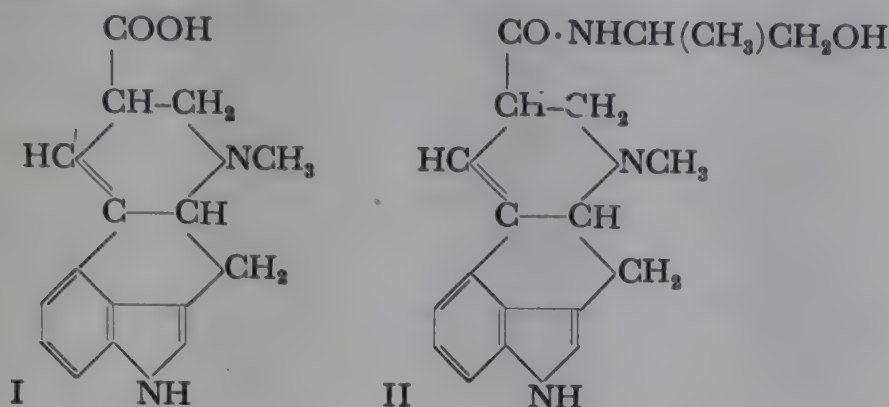
3. Ergobasine group

Ergometrine (Synonyms: Ergobasine, Ergotocine, Ergostetrine, Ergonovine)
 $C_{19}H_{23}O_2N_3$.

Ergometrinine (Ergobasinine) $C_{19}H_{23}O_2N_3$.

The investigation of the constitution of the ergot alkaloids is associated with the names of Barger, Smith and Timmis, and especially Jacobs and Craig, as well as A. Stoll. By the action of methanolic alkali on the alkaloids, a large fission product, known as *ergine*, is formed, which has been recognized as the amide of *lysergic acid*, $C_{16}H_{16}O_2N_2$.

Lysergic acid contains a double bond. Colour reactions indicate that it contains an indole group. Furthermore, 1-methyl-5-aminonaphthalene, quinoline, picric acid, and propionic acid have been obtained as degradation products. The constitutional formula (I) derived from these facts has been largely ascertained by a synthesis of *dl*-dihydrolysergic acid (W. A. Jacobs):

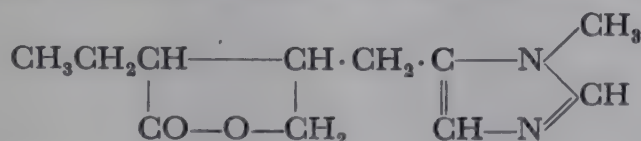


Ergometrine (ergobasine) breaks down on hydrolysis into lysergic acid, and *D*-1-hydroxy-2-aminopropane, and can also be built up again from these two compounds (Stoll and Hofmann). It is therefore a hydroxyisopropylamide of lysergic acid, and has formula II.

The basic residue combined with the lysergic acid, which in ergometrine is alaninol, has a more complex composition in the cases of ergocristine, ergotamine, etc. Jacobs and Craig, as well as Stoll and his co-workers, obtained dipeptides in addition to lysergic acid on hydrolysing these alkaloids. That from ergocristine has been further broken down into *L*(—)-phenylalanine, and *D*(+)-proline (dimethylpyruvic acid, $(\text{CH}_3)_2\text{CHCO} \cdot \text{COOH}$, is formed at the same time, perhaps as a fission product of α -hydroxyvaline, $(\text{CH}_3)_2\text{CHC}(\text{OH})\text{NH}_2 \cdot \text{COOH}$). These ergot alkaloids represent an interesting new type of alkaloid as they contain polypeptides as integral parts of the molecule, and which therefore are closely related to the proteins.

Pilocarpine, $\text{C}_{11}\text{H}_{16}\text{N}_2\text{O}_2$. Jaborandi leaves (*Pilocarpus pennatifolius*) contain several bases, of which the best-investigated is pilocarpine.

The constitutional formula advanced for this alkaloid (Pinner, Jowett)

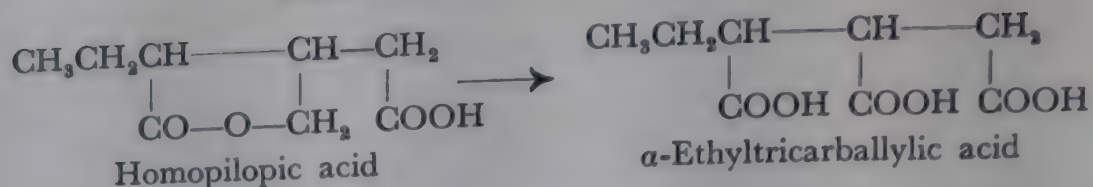


depends on the following observations:

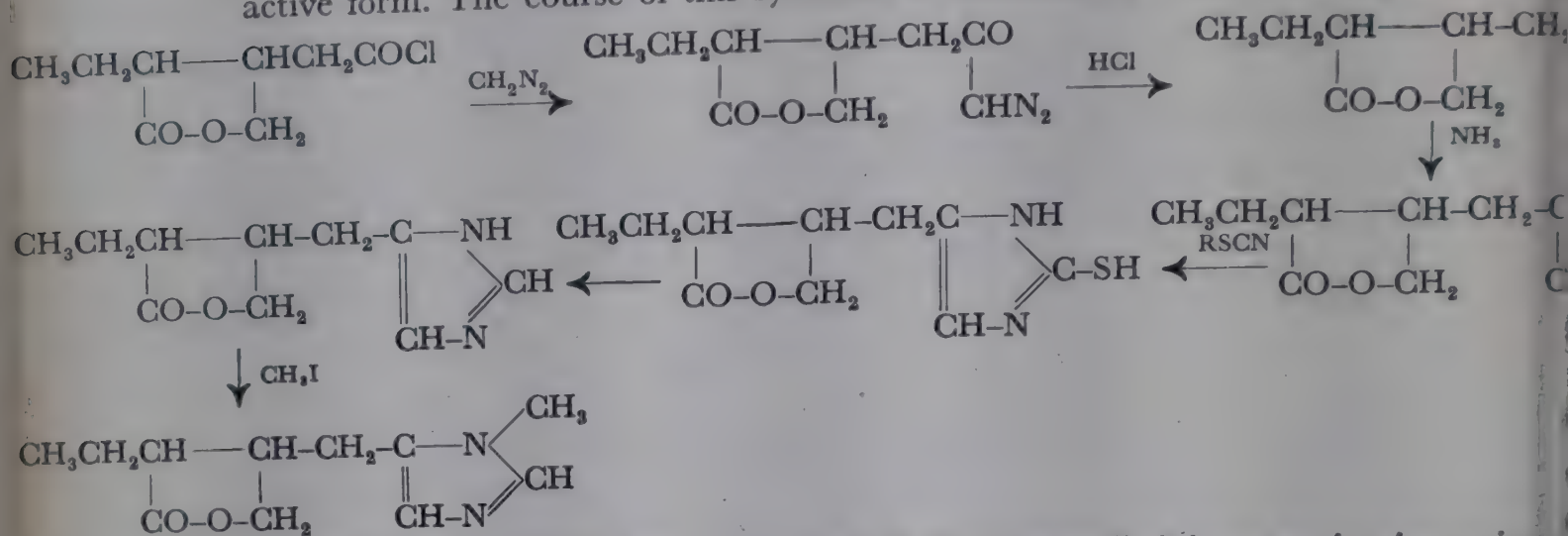
If pilocarpine is distilled with zinc dust, 1-methylglyoxaline, and 1:5-dimethylglyoxaline can be isolated:



On the other hand, the nitrogen-free half of pilocarpine can be isolated as homopilopie acid and pilopie acid by oxidizing the alkaloid with potassium permanganate or ozone. Homopilopie acid, when fused with alkali, gives α -ethyltricarballic acid:



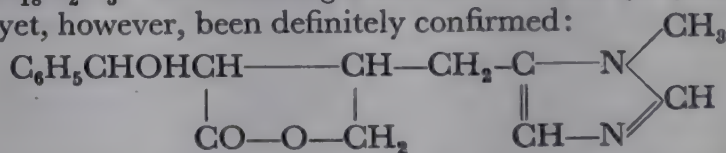
Finally, it has been possible to synthesize pilocarpine, also in an optically active form. The course of this synthesis is illustrated by the following scheme:



Pilocarpine melts at 34° ; $[\alpha]_D = +100.5^\circ$. Physiologically it is very active, increasing glandular secretions, and therefore causing increased perspiration and salivation. The peristalsis of the intestine is strengthened by pilocarpine. It produces contraction of the pupil of the eye, thus acting in just the opposite way to atropine. It is therefore used in ophthalmology. Use is also made of its power to induce perspiration.

ISOPILOCARPINE, $\text{C}_{11}\text{H}_{16}\text{N}_2\text{O}_2$. This substance is a stereoisomeride of pilocarpine. On oxidation it gives homoisopilopic acid. Pilocarpine partially isomerizes to *isopilocarpine* on heating with alcoholic potash. The change is reversible.

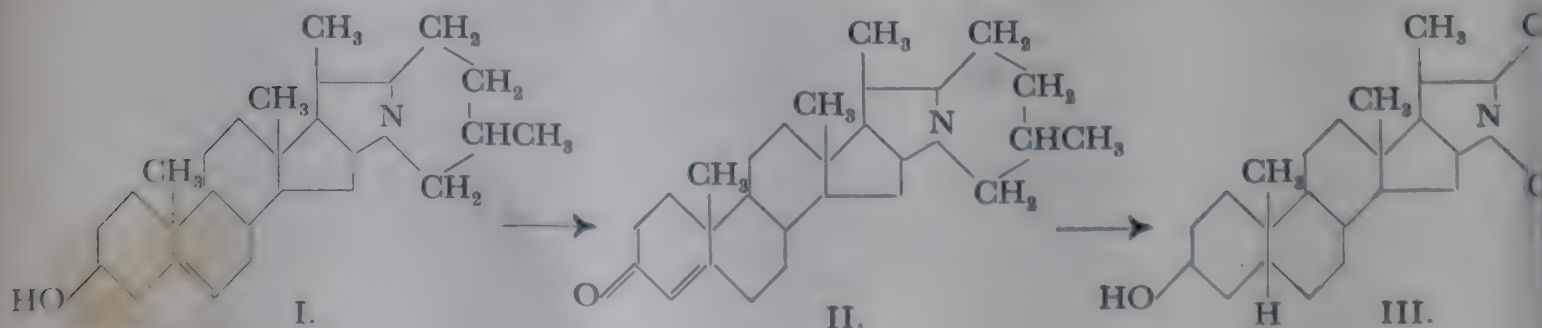
PILOSINE, $\text{C}_{16}\text{H}_{18}\text{N}_2\text{O}_3$. The following structure has been proposed for this Jaborandi alkaloid. It has not yet, however, been definitely confirmed:

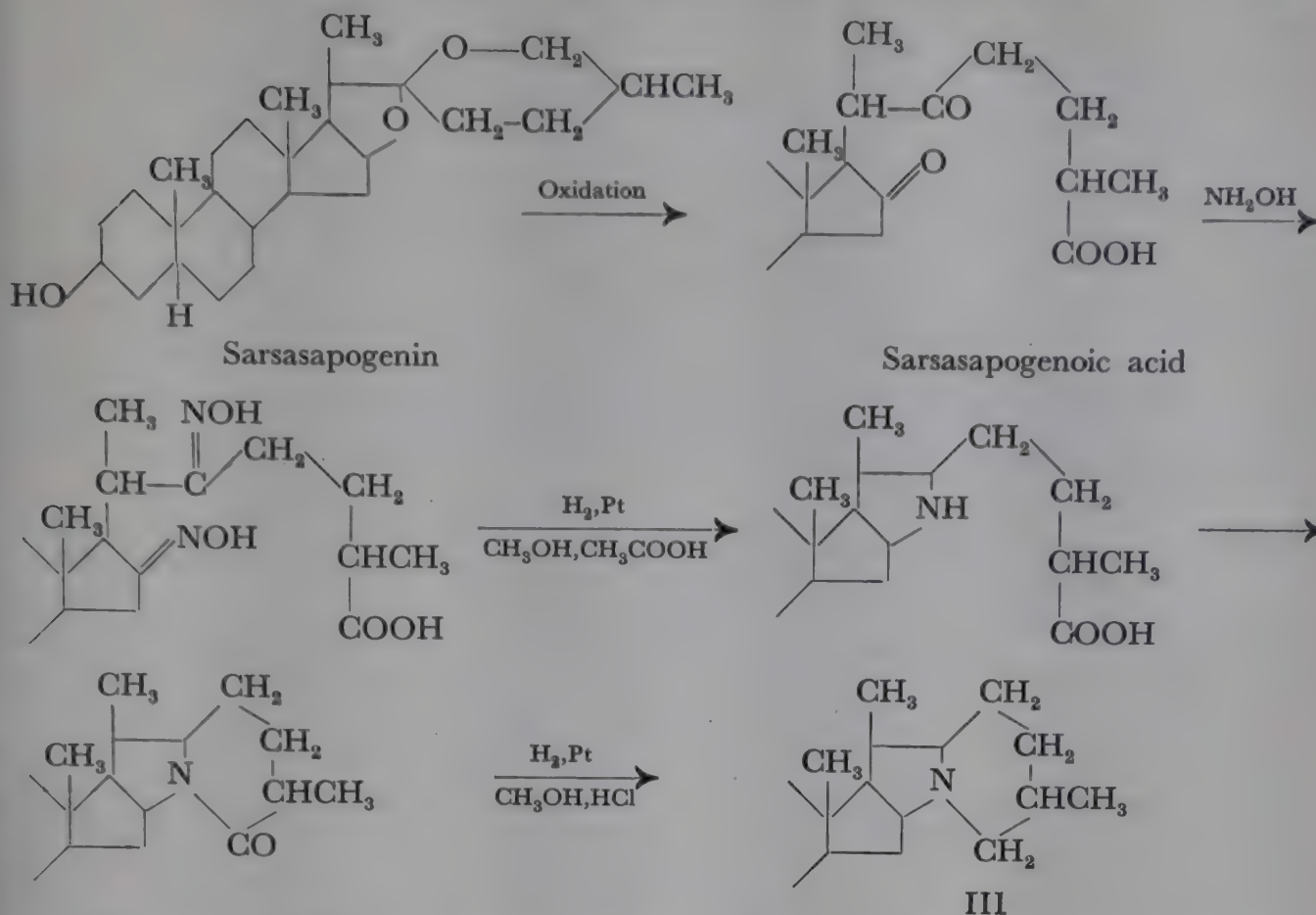


Solanine. Solanidine. Many *Solanum* species contain alkaloids which on hydrolysis are split into bases and sugars, and which are therefore also called glycoalkaloids. Of these, the best-investigated at present is solanine and its aglycone solanidine. Both occur in *Solanum tuberosum* (potato) in different parts of the plant (embryo, leaves, tubers, and berries).

On hydrolysis solanine breaks down into 1 mol. D-glucose, 1 mol. rhamnose, 1 mol. galactose, and 1 mol. solanidine, $\text{C}_{27}\text{H}_{43}\text{ON}$. The latter compound has been studied by numerous investigators (C. Schöpf, F. Bergel, A. Soltys, H. Dieterle, H. Rochelmeyer, V. Prelog, W. A. Jacob). The interesting result was obtained that the carbon skeleton of solanidine corresponds to that of the steroids. The solanine bases are thus "steroid alkaloids".

Evidence for the structure I of solanidine is, in particular, that it can be converted, through the corresponding ketone (Δ^4 -solanidenone-(3), formula II), into the reduction product *allosolanidanol*-(3 β) (formula III). The latter has also been obtained from the structurally-known sarsasapogenin in the following way:



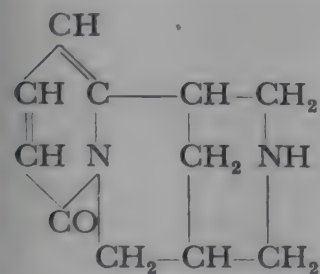


Solanine crystallizes in colourless needles, m.p. 245–250°; solanidine melts at 218–9°. Both compounds dissolve in concentrated sulphuric acid with a yellow colour which afterwards changes through red and violet to brown.

We will also deal in this chapter with other alkaloids which are of general interest on account of their physiological action, or for other reasons. The constitutions of some of them have not yet been completely elucidated.

Aconitine, $\text{C}_{34}\text{H}_{47}\text{NO}_{11}$. This occurs in *Aconitum napellus* (blue aconite). Closely related aconitines have been found in other species of aconite. They are all esters of alkalamines (aconines) with acetic acid and benzoic acid, or veratric acid. The aconines, which are probably aliphatic in nature, have several hydroxyl groups.

All the aconitines are exceedingly toxic. They act on the central nervous system, cause convulsions, and produce paralysis of the respiratory centre.

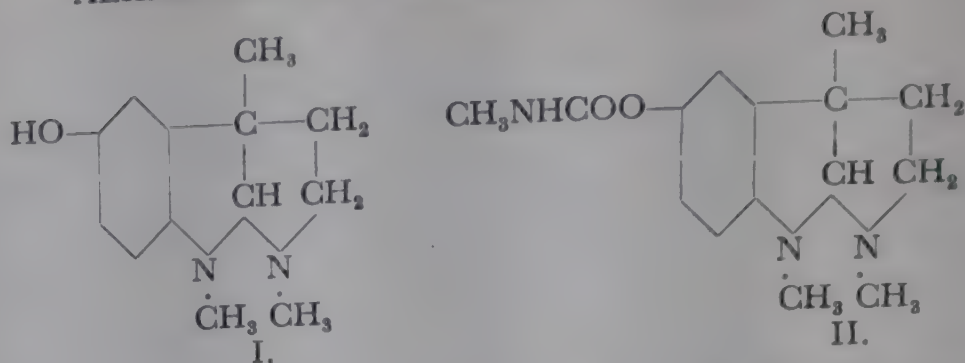


Cytisine, $\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}$. This is the alkaloid of laburnum (*Cytisus laburnum*). The substance probably has the accompanying formula (R. H. Ing, Späth). The pharmacological actions of cytisine are similar to those of nicotine; first stimulation, and then paralysis of the nervous system occurs. There is an increased flow of saliva, and increased peristaltic activity of the intestines. Poisoning has often been observed after chewing the petals and fruit of laburnum.

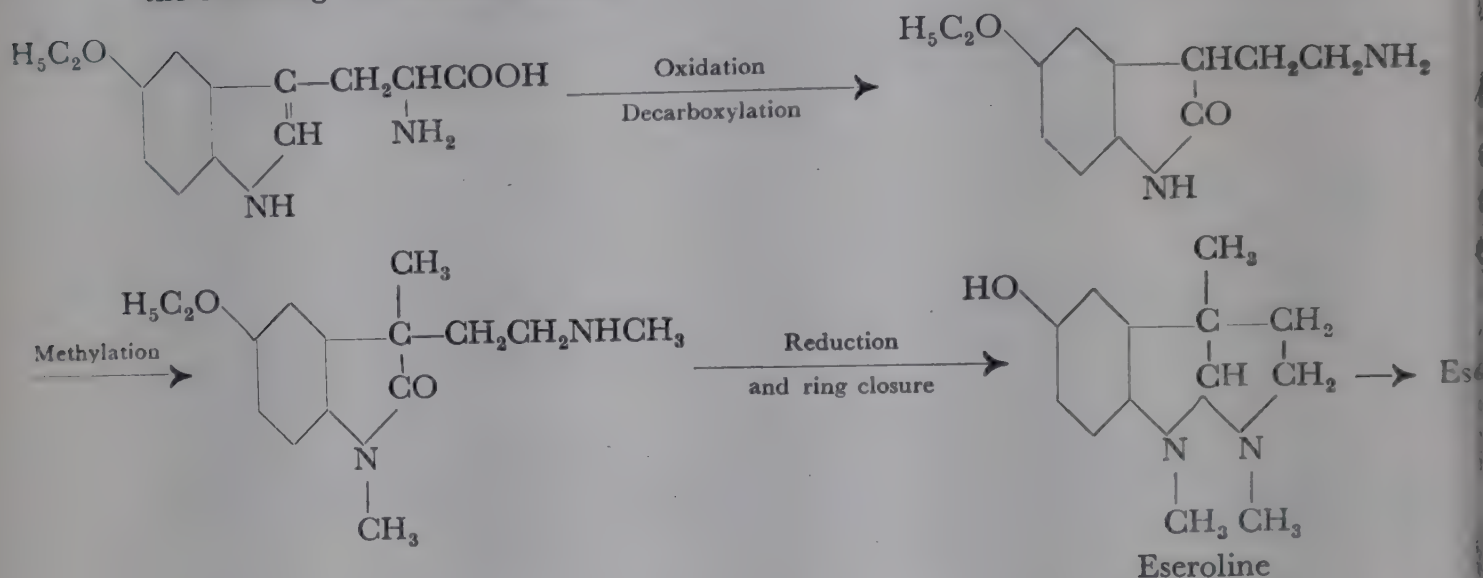
Emetine, $\text{C}_{29}\text{H}_{40}\text{N}_2\text{O}_4$. This occurs, together with *cepheline*, *psychotrine*, and other bases, in *Psychotria ipecacuanha* root. The constitution of the compound is still unknown. Probably two hydrogenated isoquinoline rings are present.

Emetine is used in medicine in cases of amoebic dysentery. Its powerful emetic action is noteworthy.

Physostigmine, or **eserine**, $\text{C}_{15}\text{H}_{21}\text{N}_3\text{O}_2$, is obtained from the Calabar bean. The alkaloid is an indole derivative. On treatment with alkalis it is decomposed into methylamine, carbon dioxide, and *eseroline*, $\text{C}_{13}\text{H}_{18}\text{N}_2\text{O}$. Its constitution has been determined through the investigations of Max and Michel Polonovski. Eseroline has formula I, and eserine formula II:



These constitutional formulæ were confirmed by the synthesis of the alkaloid by Percy Julian and J. Pikel. The synthesis starts from 5-ethoxytryptophan, and proceeds through the following intermediate stages:



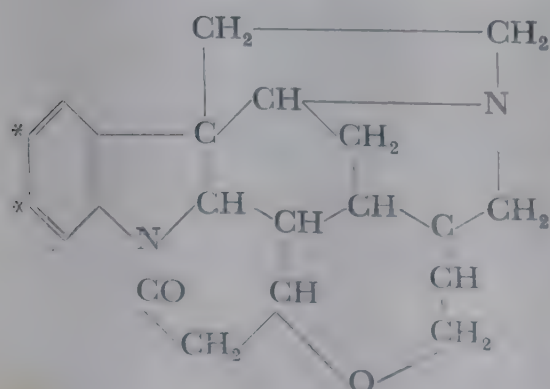
Since optically active starting materials were used, optically active eseroline, and from it, optically active physostigmine, was obtained, identical with the natural product.

It should be mentioned that the amine hydroxide of eserine (geneserine) occurs in nature.

The physiological actions of physostigmine are similar to those of pilocarpine. It causes contraction of the pupils (opposite action to that of atropine), increases glandular secretion, and increases the peristaltic activity of the intestines. It is used moreover, in ophthalmology and in veterinary work (colic of horses). The paralytic effects of the arrow-poison *curare*, are suppressed by eserine.

A synthetically produced derivative of *m*-aminophenol, *prostigmine*, $m\text{-(CH}_3)_2\text{NCOO}\cdot\text{C}_6\text{H}_4\cdot\text{N(CH}_3)_3\text{SO}_4\text{CH}_3$, acts in a similar way to physostigmine, and is at present often used as a substitute for the latter.

Strychnine, $\text{C}_{21}\text{H}_{22}\text{O}_2\text{N}_2$, and **brucine**, $\text{C}_{23}\text{H}_{26}\text{O}_4\text{N}_2$, are two closely related, very



poisonous plant bases (producing convulsions), which occur in the seeds of several varieties of *Strychnos*, and particularly abundantly in *Nuxvomica*. Brucine is a dimethoxy-derivative of strychnine. R. Robinson has proposed the accompanying formula for strychnine, which, however, still needs further confirmation. Brucine contains the two methoxyl groups at the atoms marked with an asterisk.

The ease with which these alkaloids are obtained, and their cheapness have given rise to their use for various purposes. Strychnine in particular is often used for the extermination of smaller animals (mice, rabbits), being specially useful for this purpose on account of its extreme toxicity. Furthermore, both bases are frequently used for the resolution of acidic racemic compounds into their optically active forms.

The biological formation of the alkaloids.

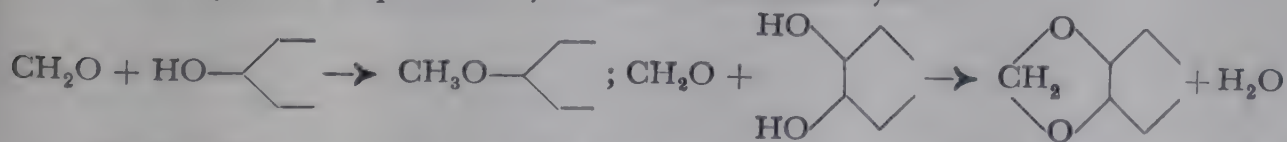
The wide occurrence of alkaloids in the vegetable kingdom suggests that they fulfil some important function in the life of the plant. Although this matter has often been discussed and also investigated experimentally it cannot be said that the solution of the problem is yet in sight. Heckel put forward the view that the alkaloids represent intermediate stages in the building up of protoplasm. If this is the case at all, this function would be confined to a few alkaloids which are related to the protein amino-acids. The great majority of the true alkaloids is not capable of being assimilated by the plant, as has been shown experimentally, and wherever their quantity during the plant growth has diminished, no corresponding increase in the protein present has been found (Lutz and Clautriau).

Other authors (especially Errera) have put forward the view that the alkaloids are protective substances for the plant. This view is based on the fact that they are frequently localized in the peripheral organs of the plant. However, it is known from experience that they often do not protect the parts concerned of the plants against lower or even higher animals. Also, the view that the alkaloids are substances which induce plant metabolism, cannot at present be supported experimentally though many believe this theory to be true.

Various workers are of the opinion that the plant bases are products of decomposition, or products of regressive metabolism, and that part of the nitrogen which is removed from the metabolism is retained by them. They thus occupy the position in plants which urea and uric acid occupy in animals. This theory too at present lacks experimental evidence. It appears not very probable, in the case of the complex, higher-molecular alkaloids, in which the nitrogen represents only an extremely small part of the whole molecule, since it can hardly be assumed that the plant would build up a complicated carbon skeleton in order to retain a single nitrogen atom.

If the question as to the purpose of the formation of the alkaloids must at present still be left open, the elucidation of their biogenesis in the plant organism has, on the other hand, undeniably made great progress. There is scarcely any doubt possible that many alkaloids (according to A. Pictet and R. Robinson, the majority) are genetically connected with protein amino-acids. In the case of simpler alkaloids, such as tyramine, ephedrine, hordenine, histamine, stachydrine, betonicine, turicine, hercynine, etc., these relationships are obvious. But also the more complicated ones may have originated from protein units by relatively simple reactions.

Without doubt, formaldehyde plays an important part in the phytochemical synthesis of alkaloids. This is even shown by the fact that very many alkaloids are methyl ethers or methylene ethers, which have very probably been produced by the methylation of phenols by means of formaldehyde:

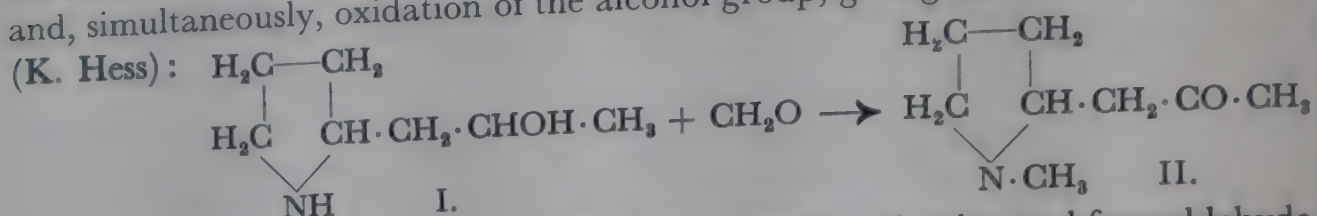


N-Methyl compounds are also very common amongst the plant bases, and they may also have been produced by the action of formaldehyde:



The oxygen set free in such methylation processes is used for parallel oxidation

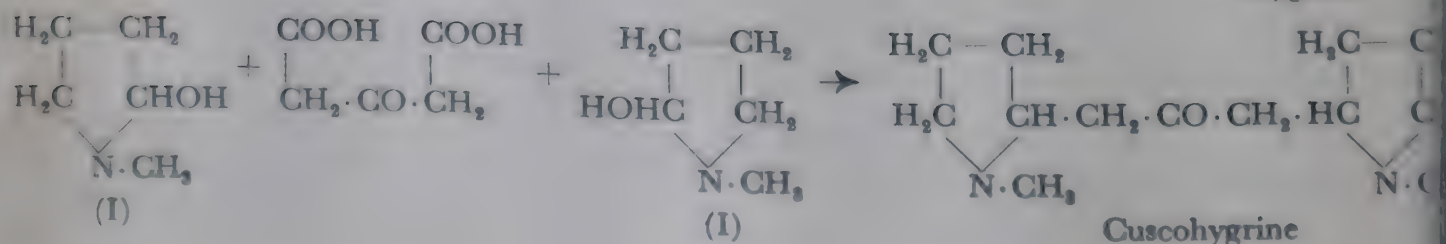
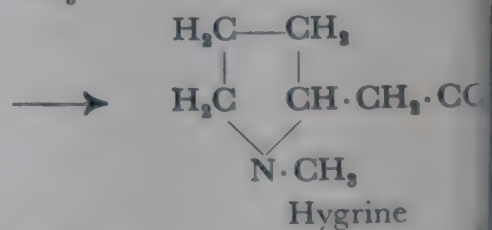
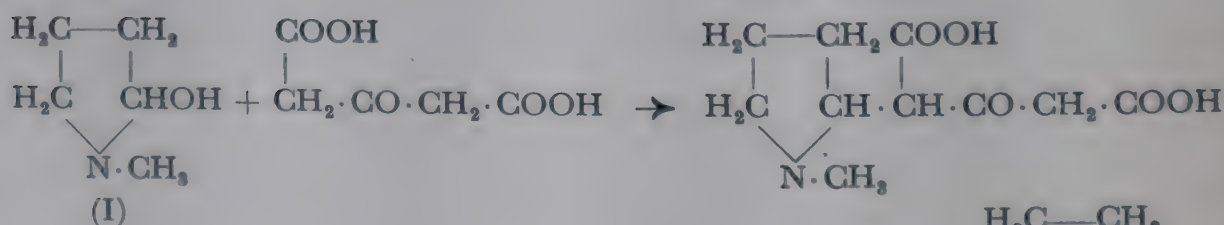
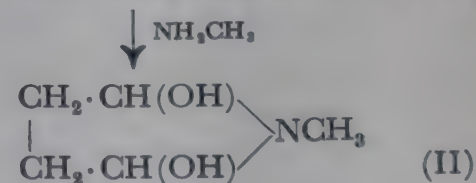
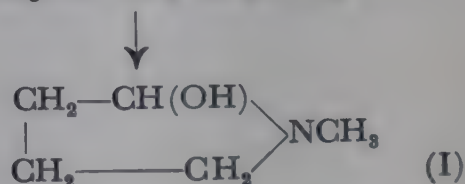
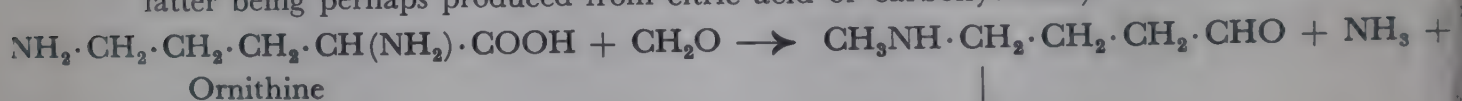
reactions. Such coupled reactions — methylation by formaldehyde and simultaneous oxidation of other groups — can also be imitated *in vitro*. For example, if the alkamine (I) is heated with formaldehyde, methylation occurs at the nitrogen, and, simultaneously, oxidation of the alcohol group, giving rise to the ketone (II) (K. Hess):

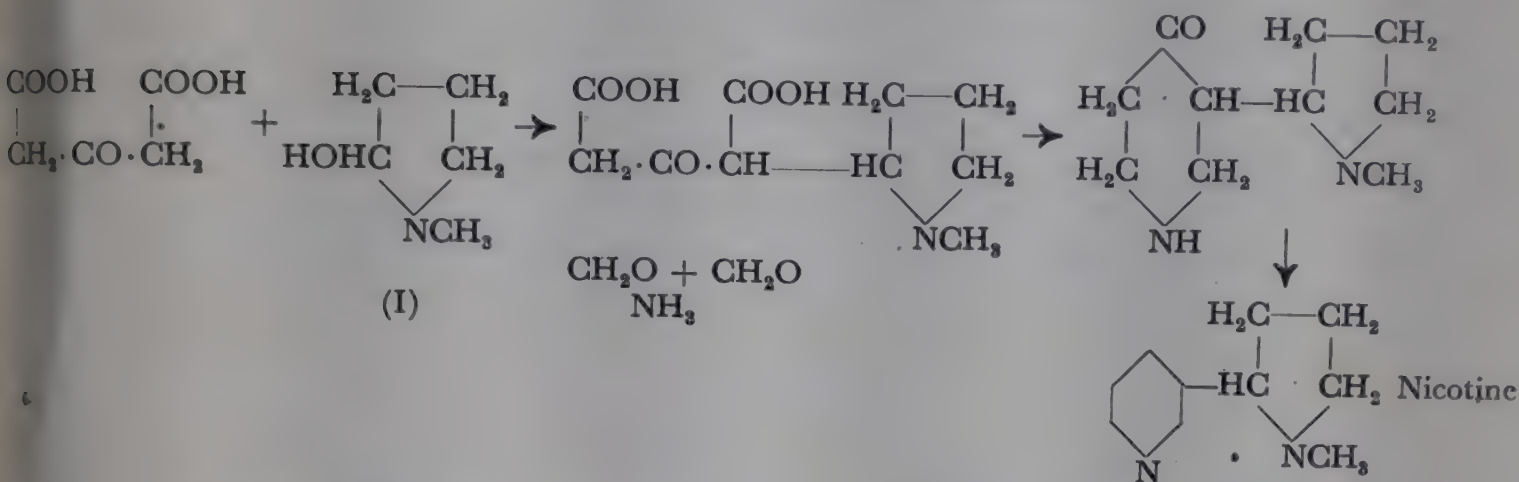
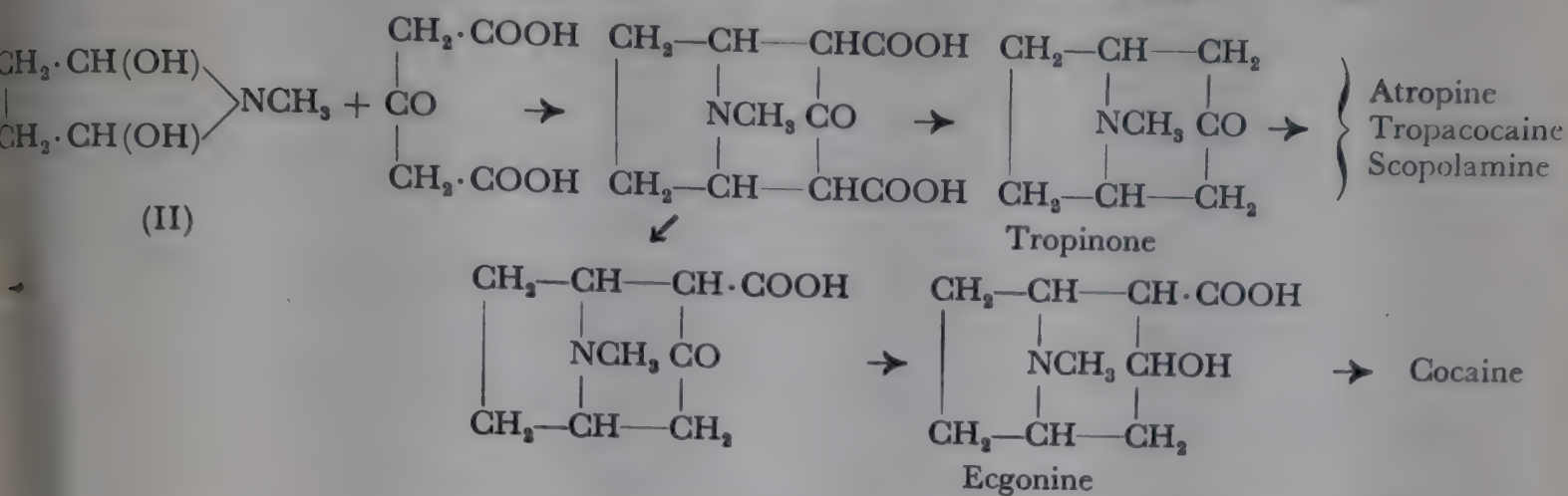


When the synthesis of *isoquinoline* from phenylethylamine and formaldehyde (or other aldehydes) was discussed, it was mentioned (p. 816) how these more complex ring systems could be built up from proteinogenic amines and formaldehyde. This reaction gives the key to the understanding of the phytochemical synthesis of the *isoquinoline* alkaloids (see p. 874 ff.). In similar ways it is possible to imagine how many other plant bases could have been produced from protein amino-acids. R. Robinson has developed a hypothesis on these lines, which however on some points has not been proved. A few examples may be given in the following scheme.

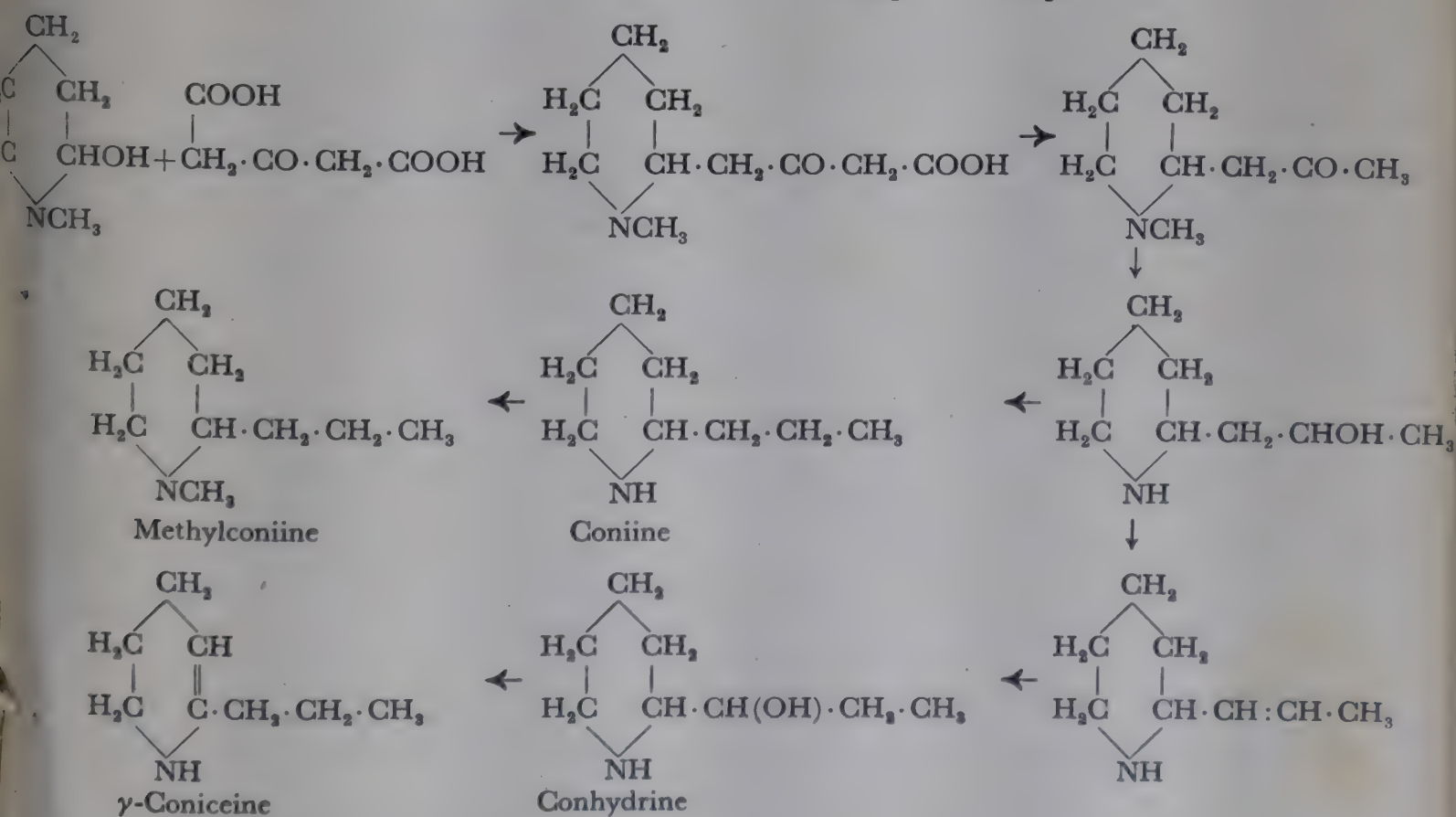
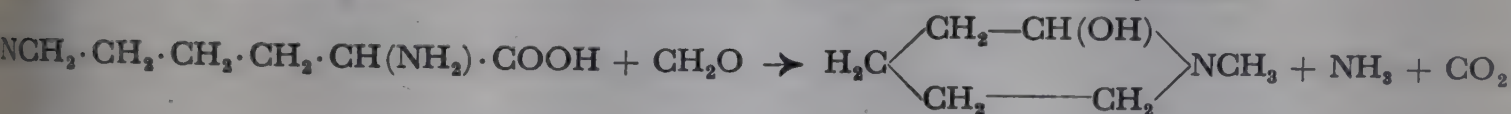
R. ROBINSON'S theory of the phytochemical synthesis of alkaloids from protein amino-acids, illustrated by the pyrrolidine and pyridine groups.

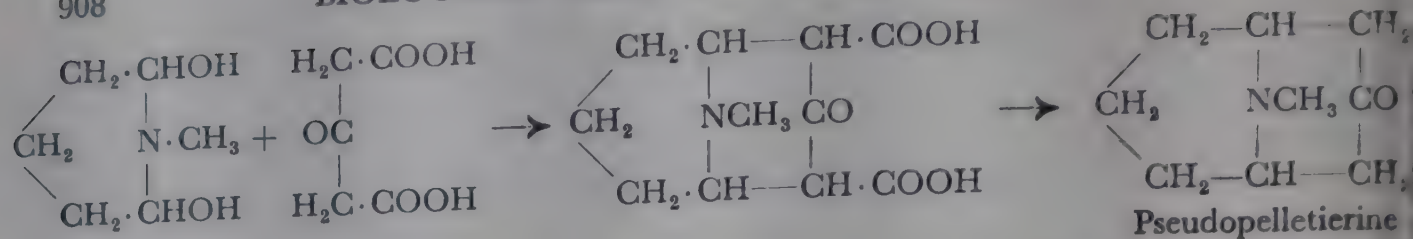
Pyrrolidine group. STARTING SUBSTANCES: *Ornithine* and *acetonedicarboxylic acid* (the latter being perhaps produced from citric acid or carbohydrates):



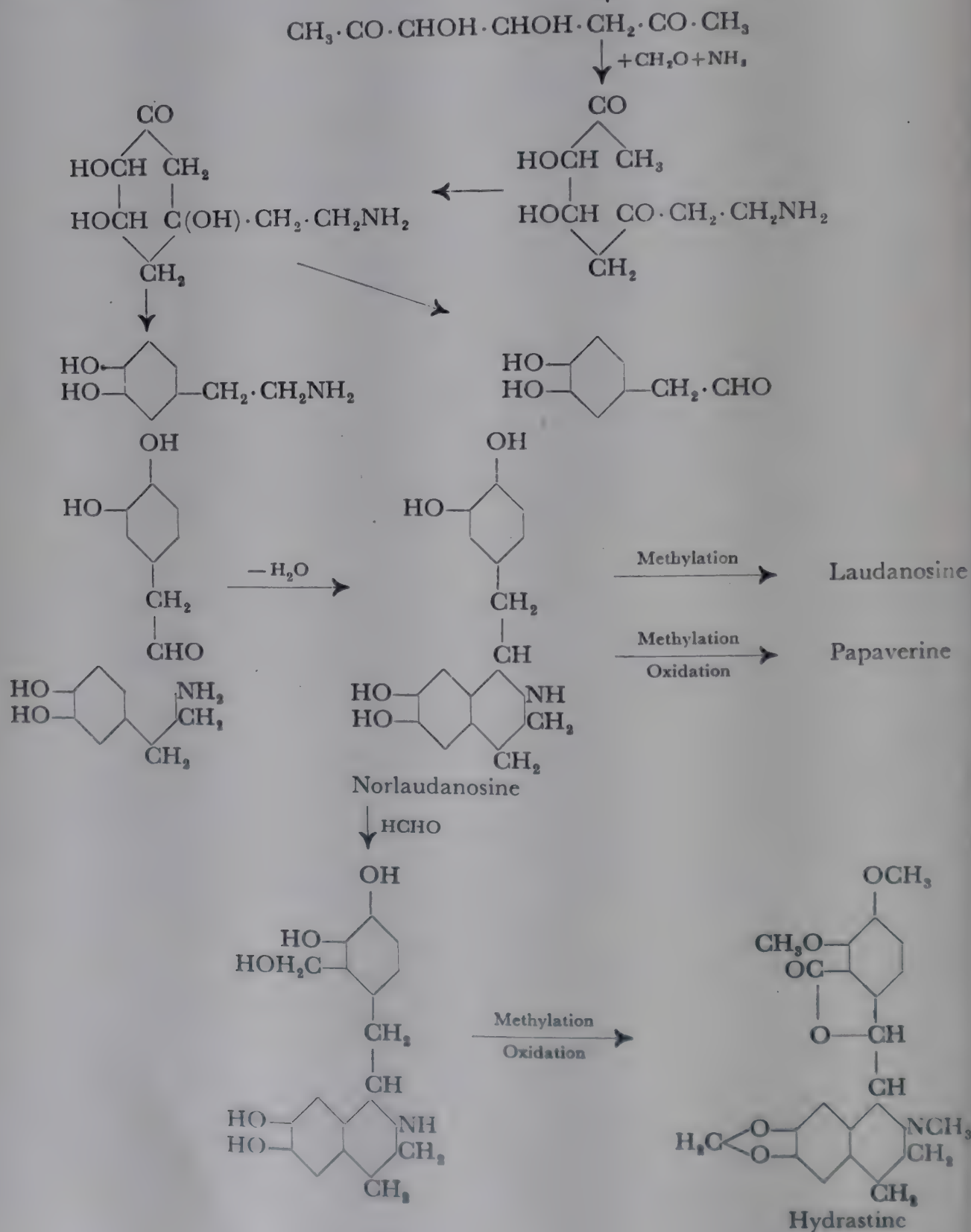
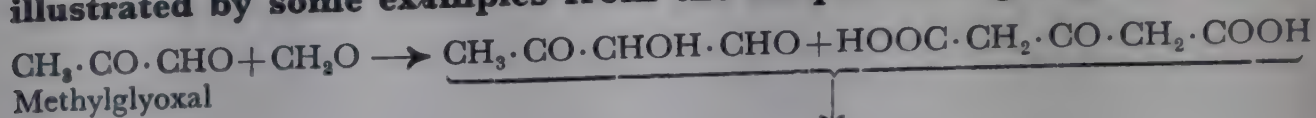


Piperidine group. STARTING SUBSTANCES: *Lysine* and *acetonedicarboxylic acid*:





R. ROBINSON'S theory of the phytochemical synthesis of alkaloids, illustrated by some examples from the isoquinoline group:



PART IV.

ORGANIC COMPOUNDS CONTAINING
ISOTOPIC ELEMENTS

CHAPTER 73

ORGANIC COMPOUNDS CONTAINING ISOTOPIC ELEMENTS

Recent research has rendered accessible a very large number of isotopes, stable and unstable (radioactive), which have found wide application also in organic chemistry. To-day, a great branch of organic and biological chemistry, of ever-increasing importance, makes use of such isotopic elements, particularly those of hydrogen, carbon, oxygen, nitrogen, phosphorus, etc. These are employed in order to characterize, or "label", definite atoms of the organic molecules. By this means it becomes possible to trace exactly the fate of these atoms in chemical and biological transformations of the substances concerned.

In chemical and physiological reactions the compounds substituted with isotopes show, in a qualitative respect, an analogous behaviour to those unsubstituted. In chemical transformations they undergo the same changes and proceed to the same places in the organism. For this reason, isotopes can serve to label those molecules whose fate in the organism or in reactions *in vitro* it is desired to follow. They are used as tracers ("indicators") to distinguish definite molecules. For the same reasons, such compounds marked by isotopes have proved to be valuable in the study of the course of chemical reactions.

The first application of the isotope technique in the investigation of processes taking place in the living cell was made by v. Hevesy in 1923 when studying the transportation and the distribution of radioactive lead in the living plant. In 1935 radioactive phosphorus, P^{32} , was used for the first time, by the same investigator, to determine the distribution and circulation of phosphorus in the rat. Since then, hundreds of similar studies have been carried out with a large variety of isotopes, in order to shed light on chemical processes, biological reactions, and technical problems. In these studies it is by no means necessary to start with compounds containing 100% of the isotope to be used in the desired place. It is generally sufficient, if a definite proportion (ca. 5–20%) of the molecules be labelled by the isotopic element introduced. For, on account of the great efficiency of isotopic analysis, even a small quantity of substance is sufficient for the detection of the isotope.

When using stable isotopes, their detection and quantitative determination are usually carried out by means of the mass-spectrograph; in rare cases (e.g. heavy hydrogen) also by measuring the specific weights of the combustion products. If the organic substance has been substituted with radioactive isotopes, the detection is easily achieved by determining the radioactivity of the substance concerned (e.g. with a Geiger-Müller counter).

1. Compounds with heavy hydrogen.

The discovery of the heavy hydrogen isotope, deuterium (D), by H. C. Urey (1932) has had a rapid and far-reaching effect on organic chemistry. It is possible, theoretically, to replace each individual hydrogen atom in every known organic compound by deuterium, and thus an immense number of new organic substances

is made accessible to investigation. Whether research will take this path and organic deuterium compounds will be synthesized in as complete a fashion as ordinary organic compounds, cannot at present be stated. This will depend to some extent upon whether ordinary organic compounds and those of deuterium differ sufficiently in chemical, physical, or physiological respects to make the preparative development of organic deuterium compounds worth while and command sufficiently great general interest.

Methods of preparation.

Essentially two groups of methods are available for the preparation of organic deuterium compounds. The one comprises those syntheses in which heavy water or heavy hydrogen is added on to unsaturated compounds, or those in which hydrolyses are carried out with heavy water. Some of these reactions are total syntheses. In the second group of methods of preparation are all those reactions in which light hydrogen, halogens, or other elements are replaced by deuterium, i.e. exchanged for it.

(a) *Preparation of organic deuterium compounds by addition of heavy water, heavy hydrogen, etc.*

The methods employed in this group resemble closely those used for obtaining ordinary organic compounds. Thus, aluminium carbide and heavy water give *methane-d₄* (CD₄) (Urey, Price); calcium carbide and deuterium oxide give *acetylene-d₂* (CD≡CD) (Randall, Barker). Grignard reagents are decomposed by heavy water with formation of deuterium compounds. Phenylmagnesium bromide gives *monodeuterobenzene* (Ingold, Wilson, etc.) when treated with heavy water. The Grignard reagents made from dibromo- and diiodobenzenes give under similar conditions *o*-, *m*-, and *p*-*dideuterobenzenes* (Redlich, Stricks). The same *mono*- and *dideuterobenzenes*, as well as *trideutero*- and *hexadeutero*-benzenes have also been prepared from the calcium salts of the corresponding benzenecarboxylic acids by pyrolysis with calcium deuterioxide (application of Dumas' hydrocarbon synthesis to carbon-deuterium compounds).

In many cases, pure heavy hydrogen is added across double bonds in unsaturated compounds, in the presence of a platinum catalyst. Thus *l*-bornylene-2 is converted into *camphane-2:3-d₂*; maleic and fumaric esters give *dideuterosuccinic acid*, HOOC·CHD·CHD·COOH; *isobutenal* and *isopentenal* diethylacetal give on reduction *isobutanal-α,β-d₂* and *isopentanal-α,β-d₂* diethylacetals (Adams). Cinnamic acid when treated with deuterium iodide, DI, is converted into *α,β-dideutero-hydrocinnamic acid*, C₆H₅CHDCHDCOOH (Erlenmeyer).

(b) *Preparation of organic deuterium compounds by exchange reactions or substitution of other atoms by deuterium.*

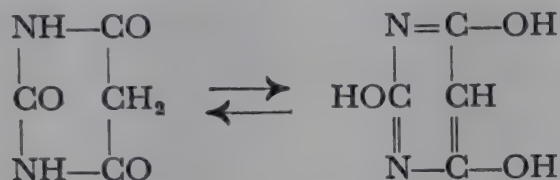
Acidic hydrogen, i.e. hydrogen atoms which are more or less ionic in character, can generally be replaced by deuterium by treatment with heavy water. Carboxyl and hydroxyl hydrogen are exchanged for deuterium under these conditions immeasurably rapidly, an equilibrium being reached as shown by the equation



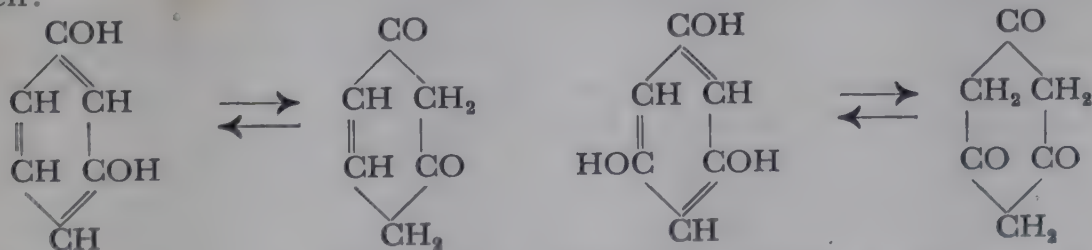
By repeated treatment with pure heavy water the deuterio compound can be obtained in a state of purity. It is noteworthy that the substitution of hydrogen

in alcoholic hydroxyl-groups, e.g. those of ethyl alcohol, mannitol (Bonhoeffer) and glucose (Harada, Titani), also takes place with immeasurable velocity, although these hydrogen atoms have no true ionic character.

Hydrogen directly linked with carbon in aliphatic and aromatic hydrocarbons in general withstands exchange by deuterium. This does not hold, however, for hydrogen atoms which are activated by proximity to negative groups, such as carbonyl, cyanide radicals, sulphonic groups, etc. Thus all four hydrogen atoms in malonic acid can be substituted by deuterium by treatment with heavy water (Münzberg). Furthermore, it can be said that in all those compounds which tend to enolize or to change into other *aci*-forms, the hydrogen atoms which are displaced in the enolization are very easily replaced by deuterium on treatment with heavy water. The following may be mentioned as examples of this kind: nitromethane, in which, as a consequence of the reversible reaction, $\text{CH}_3\text{NO}_2 \rightleftharpoons \text{CH}_2=\text{N}(\text{OH})=\text{O}$, all the hydrogen is replaceable by deuterium (Reitz); barbituric acid, which owes its reactivity to enolization as shown by the formulæ:



(Erlenmeyer); and finally some polyhydric phenols, whose reactivity with respect to heavy water must be conceived as an expression of their greater or smaller tendency to enolization. The simplest phenol takes up only extremely little deuterium into the nucleus¹, but somewhat more after addition of alkali. In the case of hydroquinone the four nuclear hydrogen atoms are substituted by deuterium only very slowly and with an approximately constant velocity, which does not agree with a continuous transformation of an enol form into the carbonyl form and *vice versa*. On the other hand, two atoms of hydrogen in the nucleus of resorcinol, and even all the nuclear hydrogen atoms in phloroglucinol can be replaced by deuterium relatively rapidly (in about 2 hours). This will be understood when it is remembered that in many reactions resorcinol (p. 437) reacts as diketocyclohexene, and phloroglucinol as triketocyclohexane (p. 440), and that in this case, hydrogen atoms oscillate between the nuclear carbon atoms and the oxygen:



The substitution by deuterium in organic substances is thus often valuable and informative in the investigation of problems of tautomerism.

By the action of catalysts or at higher temperatures also firmly bound hydrogen of organic compounds may be so much loosened, under certain circumstances, that it can be replaced by deuterium. For example, saturated fatty acids exchange

¹ 2:4:6-Tribromophenol, however, does not react at all, thus showing that in phenol the substitution of hydrogen by deuterium takes place in the *ortho*- and *para*-positions with respect to the OH-group.

the hydrogen at the α -C-atom (in concentrated sulphuric acid at elevated temperatures) for heavy hydrogen; in the presence of 1% alkali and platinum, several, possibly even all, H-atoms in saturated fatty acids are substituted at 130° by deuterium, if heavy water is allowed to act on them under these conditions.

Properties of organic compounds containing deuterium.

The *physical* properties of organic compounds containing deuterium are as a rule very similar to those of the corresponding hydrogen compounds. The melting points of the deuterium compounds are often found to be somewhat lower, and the boiling points somewhat higher than those of the corresponding substances containing hydrogen, although occasionally this may be reversed. The constants given in the literature are, moreover, not always of the same degree of reliability.

The table below gives a comparison of the boiling points and melting points of deuterium and hydrogen compounds:

BOILING POINTS.

Benzene, C_6H_6	80.12°	Hexadeuterobenzene, C_6D_6	79.4°
Chloroform, $CHCl_3$	61°	Deuteriochloroform, $CDCl_3$	61.5°
Tetrachlorethane, $CHCl_2CHCl_2$	145.2°	Tetrachlorodideuteroethane, $CDCl_2CDCl_2$	145.7°
Methyl-phenyl-methylamine, $C_6H_5CH(CH_3)NH_2$	187.4°	Methyl-phenyl-methylamine- d_2 , $C_6H_5CH(CH_3)ND_2$	188.4°

MELTING POINTS.

Benzene, C_6H_6	5.5°	Hexadeuterobenzene, C_6D_6	6.8°
		Monodeuterobenzene, C_6H_5D	6.5°
Benzoic acid, C_6H_5COOH	121.7°	Pentadeuterobenzoic acid, C_6D_5COOH	120.9°
Diethyl-carbinol, $(C_2H_5)_2CHOH$	99–99.5°	Ethyl-tetraduteroethyl-carbinol, $C_2H_5 \cdot CHOH \cdot C_2HD_4$	98.5–99°
Acetic acid, CH_3COOH	16.7°	Tetraduteroacetic acid, CD_3COOD	15.8–16°
		Trideuteroacetic acid, CD_3COOH	17.2°
		Monodeuteroacetic acid, CH_3COOD	15.4°
Malonic acid, $CH_2(COOH)_2$	133–134°	Tetradutero malonic acid, $CD_2(COOD)_2$	130–131°
Succinic acid, $HOOC(CH_2)_2COOH$	182.7–183.2°	Dideuterosuccinic acid, $(CH_2)_2(COOD)_2$	179–180°
		Tetraduterosuccinic acid, $(CD_2)_2(COOH)_2$	181–182°
		Hexadeuterosuccinic acid, $(CD_2)_2(COOD)_2$	178–179°

The densities of deuterium compounds are always somewhat greater than those of the analogous hydrogen derivatives. The following examples show this:

Benzene, C_6H_6	$d_4^{20} = 0.8784$	Hexadeuterobenzene, C_6D_6	$d_1^{20} = 0.9465$
Benzene, C_6H_6	$d_{25}^{25} = 0.8754$	Monodeuterobenzene, C_6H_5D	$d_{25}^{25} = 0.8869$
Chloroform, $CHCl_3$	$d_4^{20} = 1.4888$	Deuteriochloroform, $CDCl_3$	$d_4^{20} = 1.5004$
Tetrachlorethane, $CHCl_2CHCl_2$	$d_4^{20} = 1.5943$	Tetrachlorodideuteroethane, $CDCl_2CDCl_2$	$d_4^{20} = 1.6118$
Succinic anhydride,	$d_4^{131} = 1.2340$	Succinic anhydride- d_4	$d_1^{131} = 1.2799$

The dissociation constants of organic acids are also affected considerably when hydrogen in them is replaced by deuterium. The dissociation constant of D-acetic acid in heavy water is only one-third of that of acetic acid in water and the situation is similar for other carboxylic acids.

An interesting and often-investigated problem concerns the optical activity of deuterium compounds. Is the material difference between light and heavy hydrogen sufficient to endow a molecule of the type R_1R_2CHD with molecular asymmetry, and hence with optical activity? The question is not very easy to answer since, on account of the great similarity between hydrogen and deuterium, any expected rotation could only be small, and the resolution of racemic mixtures may present experimental difficulties for the same reason. Experiments on this problem have so far given negative results. Phenyl-phenyl- d_5 -acetic acid, $C_6H_5(C_6D_5)CHCOOH$ (Erlenmeyer), methyl-methyl- d_3 -phenylmethane, $CH_3(CD_3)CH \cdot C_6H_5$ (Burwell, Hummel, Wallis), 2-deuterocamphane (Biilmann), 2:3-dideuterocamphane (Adams), ethyl-ethyl- d_4 -carbinol, $C_2H_5 \cdot CH(OH) \cdot CD_2CHD_2$ (McGrew, Adams), and other similar compounds have not been obtained in optically active forms, or in optical isomerides of which the asymmetry is produced by deuterium atoms attached to carbon. The problem is, of course, not yet finally settled, but the difficulty of solving it is apparent.

The study of deuterium compounds promises to give much information on the mechanism of chemical reactions. Problems, which previously could scarcely be attacked by experimental methods, can, with the help of deuterium compounds, often be solved unequivocally, or have fresh light shed upon them. Two examples of this kind may conclude this short account of organic compounds containing heavy hydrogen.

According to an earlier theory the Cannizzaro reaction was assumed to take place between two aldehyde molecules in such a way that hydrogen was transferred from the hydrate of one aldehyde molecule to the other:



However, Bonhoeffer and Fredenhagen have shown that in the non-enzymatic Cannizzaro reaction which occurs with benzaldehyde in *heavy* water, benzyl alcohol is produced which contains no deuterium attached to carbon. It follows that, in contradiction to the above scheme, it is not hydroxyl hydrogen, but hydrogen from the aldehyde group $-\text{CHO}$ which is transferred to the other aldehyde molecule either directly or through an intermediate stage (see pp. 165, 257, 329).

The second example concerns the electrolysis of propionic acid in which ethylene and hydrogen are formed. The question from which part of the propionic acid molecule the hydrogen originates has been solved by the help of the deuterio-propionic acids, CD_3CH_2COOH (β -trideuteriopropionic acid) and CH_3CD_2COOH (α -dideuteriopropionic acid). Both give on electrolysis the same α, α -dideutero-ethylene, $CH_2 = CD_2$, thus proving that the hydrogen is split from the methyl group of the propionic acid, and not from the methylene group (Hölemann and Clusius).

2. Compounds with Carbon Isotopes.

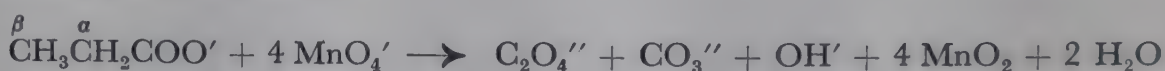
Five carbon isotopes are known to-day having the atomic weights 10, 11, 12, 13, and 14. The isotopes C^{12} and C^{13} are stable. Ordinary carbon consists of 99% C^{12} and 1% C^{13} . It has been possible to concentrate the C^{13} -isotope in fairly large quantities, so that preparations containing ca. 60% C^{13} are now available. This carbon isotope, C^{13} , is therefore frequently employed in the study of chemical and biological reactions. The measurement of the C^{13} -concentration is carried out in mass-spectrographs, specially constructed for the purpose, which allow the determination of an isotope content down to 0.02%.

Of the three radioactive carbon isotopes, C^{10} , C^{11} , and C^{14} , the first two are less suitable for use as tracers, since their half-life periods are only 8.8 seconds and 21 minutes, respectively. C^{14} , on the other hand, has a half-life period of 5,000 years. It is also very frequently used to-day, besides C^{13} , as a tracer in the investigation of chemical reactions. It can be prepared by the action of neutrons on N^{14} :



Generally, nitrogen-containing substances, such as $Ca(NO_3)_2$ or $Be(NO_3)_2$, are exposed to neutron irradiation, the C^{14} formed after some time being isolated as $BaCO_3$. As a rule, these barium carbonate preparations contain about 2% C^{14} , but some containing 20% have also been obtained.

One of first applications of isotopic carbon to the study of reaction mechanisms was in the oxidation of propionic acid by $KMnO_4$, with the formation of oxalate and carbonate:



It may be asked from which C-atoms of the propionic acid the oxalate ion arises, and from which C-atom the carbonate ion. When propionic acid containing C^{14} at the carboxyl C-atom, $CH_3CH_2C^{14}OOH$, was used, the greater part of the C^{14} -carbon was present in the oxalate obtained by the permanganate oxidation. From this it can be inferred that the fission of the propionic acid took place mainly between the α - and β -carbon atoms, and that the carbonate ion was formed chiefly from the third (β) carbon atom of the propionic acid.

A second example, in which a reaction mechanism has been elucidated by means of a carbon isotope (C^{13}), is provided by the Arndt-Eistert reaction, which has been discussed on p. 193.

When the degradation of an acid amide with alkali hypobromite (Hofmann degradation, cf. p. 130) was studied using a carboxylic acid amide which contained C^{14} -carbon in the acid amide group, radioactive CO_2 was obtained. This result confirmed the mechanism of the reaction, which had already previously been elucidated:



Phenylglyoxal is converted in alkaline solution into mandelic acid. This reaction is to be considered as an intramolecular disproportionation, or Cannizzaro reaction. When in this experiment phenylglyoxal was used, which was substituted in the α -position by C^{14} , a mandelic acid was formed containing the

radioactive carbon also in the α -position. Hence it must be concluded that the reaction proceeds without any rearrangement in the carbon chain.



The thermal decomposition of α -ketocarboxylic acids and their esters takes place, according to the results obtained with α -keto-acids containing C^{14} , in such a way that the carbon monoxide is liberated from the carboxyl group of the acid:



One of the first applications of isotopic carbon in biochemistry led to the recognition, that CO_2 is not only a final product of numerous degradation reactions taking place in microorganisms and in animal tissues, but also that it is used there in syntheses. Bacteria, yeast, and various finely-minced animal tissues were exposed to an atmosphere of CO_2 containing C^{13}O_2 . Subsequently, it could be demonstrated that C^{13}O_2 had been incorporated in organic compounds present in the biological material used. More accurate investigations showed that the isotopic carbon was contained particularly in various aliphatic hydroxy- and keto-acids, which had thus been synthesized with the taking up of the C^{13}O_2 . The first reaction probably consists in the combination of the carbon dioxide with pyruvic acid, this being a reversible process, which takes place in the cells with the help of enzymes. The reaction product formed is oxalacetic acid.



The oxalacetic acid, as discussed earlier (p. 320), can subsequently give rise to various other acids (malic, fumaric, succinic acids, etc.) in which the carbon isotope is retained.

These few examples will give an idea of the problems which may be studied and solved with the aid of carbon isotopes. It can be foreseen that this field of research will develop and expand enormously in the future, particularly in regard to its applications to biochemical and biological problems.

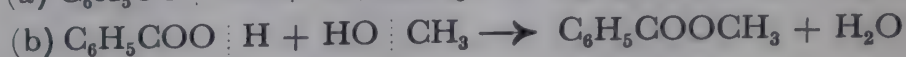
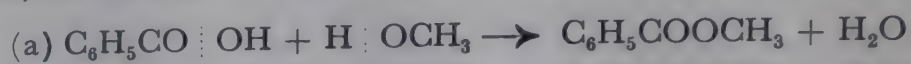
3. Compounds with Heavy Oxygen.

The oxygen isotope O^{18} is not yet available in the pure state for preparative purposes and hence no *pure* organic compounds containing heavy oxygen are known so far. However, in recent times, oxygen compounds containing an increased proportion of this isotope have been prepared and investigated. Thus similar possibilities for studying chemical reactions have been opened up as in the case of the chemistry of organic deuterium and isotopic carbon compounds.

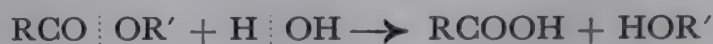
Thus a series of investigations has already been carried out with the object of studying the exchange of light oxygen for heavy oxygen. In urea and citric acid no exchange takes place at 25° by the action of water in which O^{18} has been concentrated, but in citric acid even at 75° the O^{16} is largely replaced by O^{18} . With benzaldehyde at 25° there is 31% exchange at the end of 1 hour, 62% in

4 hours, and even complete exchange after 100 hours. Glucose and fructose also exchange one oxygen atom (probably the one of the aldehyde group) for O^{18} , when they are boiled with water containing a higher percentage of the isotope O^{18} .

With the aid of heavy oxygen compounds an interesting insight has been gained into the mechanism of the processes of saponification and esterification of carboxylic acids. The esterification of a carboxylic acid (e.g. benzoic acid) with methanol, which is catalysed by acids, may take place according to the equations (a) or (b):



However, when ordinary benzoic acid reacts with methyl alcohol having an increased percentage (0.372%) of O^{18} , the formation of ordinary water only is observed. The oxygen of the water produced during the esterification therefore originates from the benzoic acid and not from the methanol, and hence the esterification process must have taken place according to equation (a). This agrees with the observation, that in the hydrolysis of esters with water containing O^{18} , the O^{18} enters the acid, non-alcoholic product of the hydrolysis. The hydrolysis thus according to the takes place equation:



It is to be expected that the organic compounds with heavy oxygen will prove useful in the solution of many other similar problems.

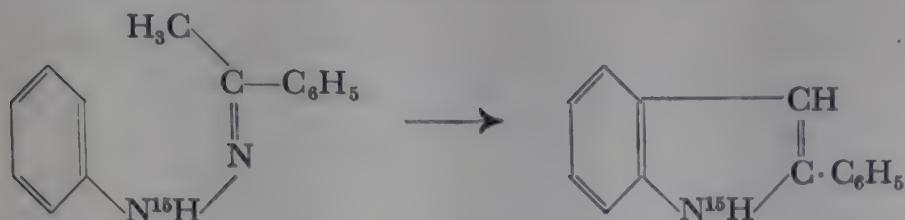
4. Compounds with Nitrogen Isotopes.

The nitrogen isotope N^{15} has so far chiefly been used in biological chemistry for the study of metabolic processes, in particular those concerning amino-acids and proteins. Very interesting and, in part unexpected, relationships have thus been discovered. For example, when an ammonium salt (ammonium citrate) containing N^{15} was administered to rats, this isotope was partly found again in various amino-acids, which were subsequently isolated from the rat organism (e.g. in glycine, creatine, glutamic acid, aspartic acid, proline, histidine, lysine, arginine). Hence the ammonium salt had, at least partially, been assimilated by the rat. Furthermore, it has been shown (R. Schoenheimer) that, after feeding certain amino-acids with a N^{15} -content to rats, the isotopic nitrogen is later found again in numerous other amino-acids which are isolated from the proteins of these animals. From this it follows that in animal metabolism "transaminations" take place to a large extent, and that there is a continual opening and closing of peptide linkages.

The following example will show how N^{15} can be used to elucidate a chemical reaction mechanism. Fischer's indole synthesis (cf. p. 784-5) was carried out starting with phenylhydrazine, in which the nitrogen linked to the phenyl group was N^{15} . This was prepared in the following way:

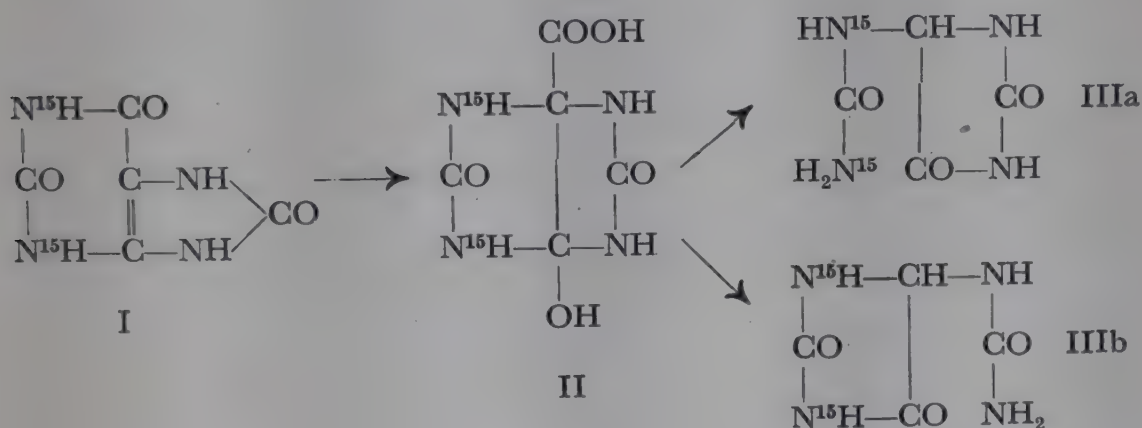


From this phenylhydrazine and acetophenone, *via* the phenylhydrazone, 2-phenylindole was obtained which still contained all the N^{15} :



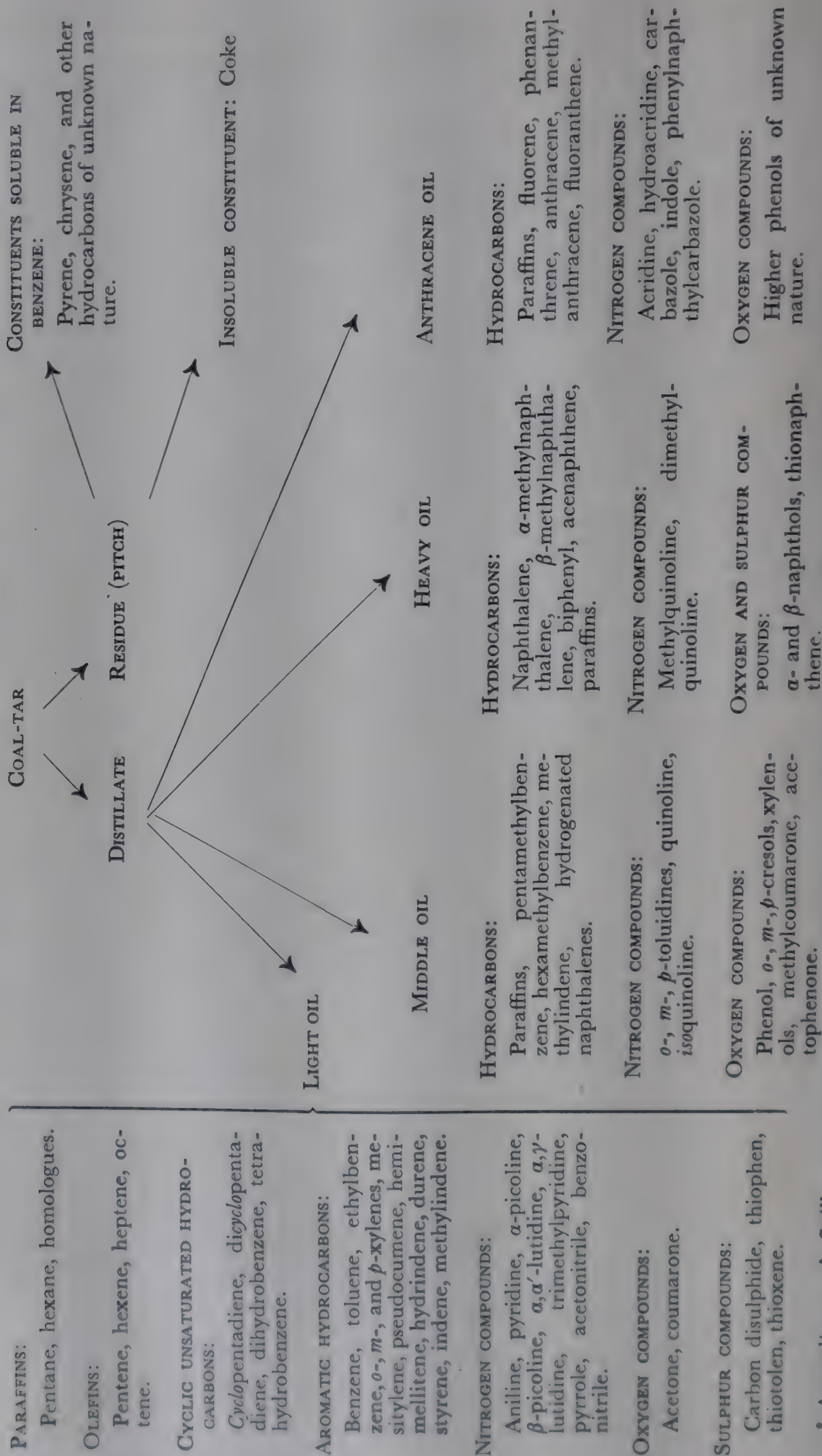
It is thus proved that in the formation of indole the nitrogen atom which has been split off is the one further removed from the aromatic ring. (C. F. H. Allen and C. V. Wilson). (For the theory of this indole formation, see also p. 785).

Another example, illustrating the usefulness of the nitrogen isotope N^{15} in the elucidation of a reaction mechanism, is the degradation of uric acid, having two N^{15} -atoms in the positions 1:3 (formula I), to allantoin (formula III). Corresponding to the following reaction scheme, N^{15} has been detected in all of the nitrogen atoms of allantoin (III). From this it can be concluded that the oxidative degradation of uric acid proceeds through the symmetrical intermediate product II. Ring fission of the latter can yield IIIa as well as IIIb. (Cf. also p. 822).



TABLES

I. The principal compounds occurring in coal tar*



* According to A. Spilker.

II. The compounds definitely detected in coal-tar, arranged in the order of their boiling points¹

Name	Formula	B.p. 760 mm °C	M.p. °C	Discoverer	Year	Literature
1:3-Butadiene	C ₄ H ₆	+1	—	Caventou	1873	Meyer, Jacobson Org.Chem.1(I),884
Pentane	C ₅ H ₁₂	39	—	Schorlemmer	1862	Ann. 125, 105
Cyclopentadiene	C ₅ H ₆	41	—	Kraemer, Spilker	1896	Ber. 29, 552
Carbon disulphide	CS ₂	47	—	Helbing	1874	Ann. 172, 281
Acetone	C ₃ H ₆ O	56	—	K. E. Schulze	1887	Ber. 20, 411
Hexane	C ₆ H ₁₄	69	—	Schorlemmer	1862	Ann. 125, 107
Hexene	C ₆ H ₁₂	69	—	Williams	1858	Ann. 108, 384
Acetonitrile	C ₂ H ₃ N	79	—41	Vincent, Delachanal	1880	Bull. soc. chim. 33, 405
Methyl ethyl ketone	C ₄ H ₈ O	80	—	K. E. Schulze	1887	Ber. 20, 411
Benzene	C ₆ H ₆	81.1	+5	A. W. Hofmann	1845	Ann. 55, 204
Thiophen	C ₄ H ₄ S	84	—	V. Meyer	1883	Ber. 17, 1471
Heptane	C ₇ H ₁₆	98	—	Schorlemmer	1862	Ann. 125, 103
Toluene	C ₇ H ₈	111	—	Mansfield	1848	Chem. Soc. 1, 244
Thiotolene	C ₅ H ₆ S	113	—	V. Meyer, Kreis	1884	Ber. 17, 787
Pyridine	C ₅ H ₅ N	117	—	Greville, Williams	1854	Jahresber. f. Chem. p. 492
Octane	C ₈ H ₁₈	119	—	Schorlemmer	1861	Ann. 125, 105
Pyrrole	C ₄ H ₅ N	133	—	Runge	1834	Poggend. Ann. 31, 67
Ethylbenzene	C ₈ H ₁₀	134	—	Noelting, Palmer	1891	Ber. 24, 1955
α -Picoline	C ₈ H ₇ N	135	—	Anderson	1846	Ann. 60, 86
Thioxene	C ₆ H ₆ S	137	—	K. E. Schulze	1884	Ber. 17, 2852
β -Picoline	C ₈ H ₇ N	138	—	Mohler	1888	Ber. 21, 1009
p -Xylene	C ₈ H ₁₀	138	+15	R. Fittig	1870	Ann. 153, 265
m -Xylene	C ₈ H ₁₀	139	—	R. Fittig	1870	Ann. 153, 265
n -Propionic acid	C ₃ H ₆ O ₂	141	—24	Kruber, Morneweg	1938	Ber. 71, 2485
o -Xylene	C ₈ H ₁₀	143	—	Jacobsen	1877	Ber. 10, 1010
2:6-Lutidine	C ₇ H ₉ N	143	—	Lunge, Rosenberg	1887	Ber. 20, 130
Styrene	C ₈ H ₈	145	—	Berthelot	1867	Ann. Suppl. 5, 367
2:4-Lutidine	C ₇ H ₉ N	157	—	Lunge, Rosenberg	1887	Ber. 20, 131
n -Propylbenzene	C ₉ H ₁₂	159	—	G. Schultz	1909	Ber. 42, 3617
o -Ethyltoluene	C ₉ H ₁₂	159	—	G. Schultz	1909	Ber. 42, 3613
m -Ethyltoluene	C ₉ H ₁₂	159	—	G. Schultz	1909	Ber. 42, 3613
p -Ethyltoluene	C ₉ H ₁₂	162	—	G. Schultz	1909	Ber. 42, 3613
Mesitylene	C ₉ H ₁₂	164	—	Fittig, Wackenroder	1869	Ann. 151, 292
Collidine	C ₈ H ₁₁ N	165	—	Ahrens	1896	Ber. 29, 2998
Pseudocumene	C ₉ H ₁₂	168	—	Beilstein, Högler	1866	Ann. 137, 317
Coumarone	C ₈ H ₆ O	169	—	Kraemer, Spilker	1890	Ber. 23, 78
Decane	C ₁₀ H ₂₂	170	—	Jacobsen	1876	Ann. 184, 205
Hemimellitene	C ₉ H ₁₂	175	—	Jacobsen	1886	Ber. 19, 2513
Hydrindene	C ₉ H ₁₀	177	—	Moschner	1900	Ber. 33, 137
Indene	C ₉ H ₈	181	—2	Kraemer, Spilker	1890	Ber. 23, 3276
Phenol	C ₆ H ₆ O	181	42	Runge	1834	Poggend. Ann. 31, 69; 32, 308
Aniline	C ₆ H ₇ N	182	—8	Runge	1834	Poggend. Ann. 31, 65; 32, 351
o -Cresol	C ₇ H ₈ O	191	32	Southworth	1873	Ann. 168, 275

¹ According to a compilation of the Gesellschaft für Teerverwertung (Duisberg-Meiderich), completed by the author since 1928.

Name	Formula	B.p. 760 mm °C	M.p. °C	Discoverer	Year	Literature
Methylcoumarone	C_9H_8O	190	—	<i>Stoermer, Boes</i>	1900	Ber. 33, 3013
Durene	$C_{10}H_{14}$	192	80	<i>K. E. Schulze</i>	1885	Ber. 18, 3032
Benzonitrile	C_7H_5N	196	—	<i>Kraemer, Spilker</i>	1890	Ber. 23, 83
<i>o</i> -Toluidine	C_7H_9N	197	—	<i>O. Kruber, L. Rappen</i>	1940	Ber. 73, 1178
<i>m</i> -Toluidine	C_7H_9N	199	—	<i>O. Kruber, L. Rappen</i>	1940	Ber. 73, 1178
<i>p</i> -Toluidine	C_7H_9N	199	43.9	<i>O. Kruber, L. Rappen</i>	1940	Ber. 73, 1178
<i>p</i> -Cresol	C_7H_8O	201	36	<i>Kolbe, Thiemann</i>	1860	Ann. 115, 263; Ber. 11, 783
<i>m</i> -Cresol	C_7H_8O	202	+10.9	<i>Biedermann, Thiemann</i>	1873	Ber. 6, 323; 11, 783
Acetophenone	C_8H_8O	202	20	<i>Weissgerber</i>	1903	Ber. 36, 754
Hydronaphthalene	$C_{10}H_{12}$	205	—	<i>Berthelot</i>	1867	Ann. Suppl. 5, 371
1:3:4-Xylenol	$C_8H_{10}O$	208.5 -210	26	<i>Goldschmidt</i>		M. 28, 1091
1:4:5-Xylenol	$C_8H_{10}O$	208.5 -210	75	<i>Moehrle</i>	1926	D.R.P. 447,540
2:4-Dimethylaniline	$C_8H_{11}N$	212	—	<i>O. Kruber, L. Rappen</i>	1940	Ber. 73, 1178
1:2:3-Xylenol	$C_8H_{10}O$	214	75	<i>Brückner</i>	1928	Z. ang. Chem. 41, 1043
<i>p</i> -Xylidine	$C_8H_{11}N$	215	—	<i>O. Kruber, L. Rappen</i>	1940	Ber. 73, 1178
<i>m</i> -Ethylphenol	$C_8H_{10}O$	217	—	<i>Kruber, Schmitt</i>	1931	Ber. 64, 2270
<i>p</i> -Ethylphenol	$C_8H_{10}O$	218	45	<i>Kruber, Schmitt</i>	1931	Ber. 64, 2270
Naphthalene	$C_{10}H_8$	218	80	<i>Kidd</i>	1824	Berz. Jahrb. 3, 186
1:3:5-Xylenol	$C_8H_{10}O$	219	68	<i>K. E. Schulze</i>	1887	Ber. 20, 410
Thionaphthene	C_8H_6S	220	32	<i>Weissgerber, Kruber</i>	1920	Ber. 53, 1551
Dimethylcoumarone	$C_{10}H_{10}O$	221	—	<i>Stoermer, Boes</i>	1900	Ber. 33, 3013
3:5-Dimethylaniline	$C_8H_{11}N$	222	—	<i>O. Kruber, L. Rappen</i>	1940	Ber. 73, 1178
2:3-Dimethylaniline	$C_8H_{11}N$	223	—	<i>O. Kruber, L. Rappen</i>	1940	Ber. 73, 1178
1:2:4-Xylenol	$C_8H_{10}O$	225	65	<i>K. E. Schulze</i>	1887	Ber. 20, 410
Symm. <i>m</i> -Methyl-ethylphenol	$C_9H_{12}O$	232.5 -234.5	55	<i>Kruber, Schmitt</i>	1931	Ber. 64, 2270
<i>iso</i> Pseudocumenol	$C_9H_{12}O$	233	95-96	<i>Kruber, Schmitt</i>	1931	Ber. 64, 2270
1:2:3:4-Tetramethylpyridine	$C_9H_{13}N$	233	—	<i>Ahrens</i>	1895	Ber. 28, 795
Quinoline	C_9H_7N	239	—	<i>Runge, Fischer</i>	1834	Poggend. Ann. 31, 65, 513
<i>Iso</i> quinoline	C_9H_7N	240	28	<i>Hoogewerff, van Dorp</i>	1885	Rec. d. Trav. Pays-Bas 4, 125
7-Hydroxycoumarone	$C_8H_6O_2$	240	43	<i>Kruber, Schmieden</i>	1939	Ber. 72, 653
β -Methylnaphthalene	$C_{11}H_{10}$	241	33	<i>K. E. Schulze</i>	1884	Ber. 17, 842
α -Methylnaphthalene	$C_{11}H_{10}$	245	—	<i>K. E. Schulze</i>	1884	Ber. 17, 842
4-Hydroxyhydrindene	$C_9H_{10}O$	245	50	<i>Kruber, Schmieden</i>	1939	Ber. 72, 653
2-Methylquinoline	$C_{10}H_9N$	247	—	<i>Jacobsen, Reimer</i>	1883	Ber. 16, 1082

Name	Formula	B.p. 760 mm °C	M.p. °C	Discoverer	Year	Literature
Durenol	$C_{10}H_{14}O$	247– 248	118–119	Kruber	1931	Ber. 64, 2270 D.R.P. 454,696
8-Methylquino- line	$C_{10}H_9N$	247	—	Jantzen	1932	Habil.-Schrift Hamburg
3:4:5-Trimethyl- phenol	$C_9H_{12}O$	248	106	Kruber, Marx	1940	Ber. 73, 1175
Paraffin	$C_{18}H_{38}$	250	20	K. E. Schulze	1887	Ber. 20, 410
Benzoic acid	$C_6H_6O_2$	250	121	Kruber, Morneweg	1938	Ber. 71, 2485
5-Hydroxy- hydrindene	$C_9H_{10}O$	251	55	Kruber	1940	Z. ang. Chem. 53, 72
3-Methyl- isoquinoline	$C_{10}H_9N$	252	—	Jantzen	1932	Habil.-Schrift Hamburg
Indole	C_8H_7N	253	53	Weissgerber	1910	Ber. 43, 3520
Biphenyl	$C_{12}H_{10}$	254	70.5	Büchner	1875	Ber. 8, 23
1-Methyl- isoquinoline	$C_{10}H_9N$	255	—	Jantzen	1932	Habil.-Schrift Hamburg
2:8-Dimethyl- quinoline	$C_{11}H_{11}N$	255	—	Jantzen	1932	Habil.-Schrift Hamburg
β -Ethyl- naphthalene	$C_{12}H_{12}$	256	—	Kruber, Schade	1936	Ber. 69, 1722
7-Methyl- quinoline	$C_{10}H_9N$	257	—	Jantzen	1932	Habil.-Schrift Hamburg
6-Methyl- quinoline	$C_{10}H_9N$	258	—	Jantzen	1932	Habil.-Schrift Hamburg
3-Methyl- quinoline	$C_{10}H_9N$	259	—	Jantzen	1932	Habil.-Schrift Hamburg
2:6-Dimethyl- naphthalene	$C_{12}H_{12}$	261	110	Weissgerber, Kruber	1919	Ber. 52, 355
1:6-Dimethyl- naphthalene	$C_{12}H_{12}$	262	—	Weissgerber, Kruber	1919	Ber. 52, 348
2:7-Dimethyl- naphthalene	$C_{12}H_{12}$	262	96	Weissgerber, Kruber	1919	Ber. 52, 364
5-Methyl- quinoline	$C_{10}H_9N$	262	—	Jantzen	1932	Habil.-Schrift Hamburg
1:3-Dimethyl- quinoline	$C_{11}H_{11}N$	262	—	Jantzen	1932	Habil.-Schrift Hamburg
1:7-Dimethyl- naphthalene	$C_{12}H_{12}$	262	—	Kruber	1936	Ber. 69, 1722
1:3-Dimethyl- isoquinoline	$C_{11}H_{11}N$	262	30	Jantzen	1932	Habil.-Schrift Hamburg
4-Methyl- quinoline	$C_{10}H_9N$	264	—	Pforte	1925	Diss. Hamburg
3-Methylindole	C_9H_9N	265	95	Kruber	1926	Ber. 59, 2752
2:3-Dimethyl- naphthalene	$C_{12}H_{12}$	265	104	Weissgerber	1919	Ber. 52, 370
1:5-Dimethyl- naphthalene	$C_{12}H_{12}$	265	82	Kruber, Marx	1939	Ber. 72, 1970
1:2-Dimethyl- naphthalene	$C_{12}H_{12}$	266	—	Kruber, Schade	1935	Ber. 68, 11
7-Methylindole	C_9H_9N	266	85	Kruber	1926	Ber. 59, 2752
5-Methylindole	C_9H_9N	267	60	Kruber	1926	Ber. 59, 2752
4-Methylindole	C_9H_9N	267	5	Kruber	1929	Ber. 62, 2877
<i>m</i> -Methyl- biphenyl	$C_{13}H_{12}$	269	—	Kruber	1932	Ber. 65, 1382
<i>o</i> -Methyl- biphenyl	$C_{13}H_{12}$	271	48	Kruber	1932	Ber. 65, 1382
<i>p</i> -Methyl- biphenyl	$C_{13}H_{12}$	271	48	Kruber	1932	Ber. 65, 1382

Name	Formula	B.p. 760 mm °C	M.p. °C	Discoverer	Year	Literature
2-Methylindole	C_9H_9N	271–272	61	<i>Kruber</i>	1926	Ber. 59, 2877
Acenaphthene	$C_{12}H_{10}$	278	95	<i>Berthelot</i>	1867	Ztschr. ang. Chem. 1867, p. 714
α -Naphthol	$C_{10}H_8O$	280	96	<i>K. E. Schulze</i>	1884	Ann. 227, 143
1:3:7-Trimethyl- naphthalene	$C_{13}H_{14}$	280	13.5	<i>Kruber</i>	1939	Ber. 72, 1972
2:3:5-Trimethyl- naphthalene	$C_{13}H_{14}$	285	25.3	<i>Kruber</i>	1940	Ber. 73, 1174
2:3:6-Trimethyl- naphthalene	$C_{13}H_{14}$	286	102	<i>Kruber</i>	1939	Ber. 72, 1972
Biphenylene oxide	$C_{12}H_8O$	287	90	<i>Kraemer, Weissgerber</i>	1901	Ber. 34, 1662
2:4:6-Trimethyl- quinoline	$C_{12}H_{13}N$	288	50	<i>Kruber</i>	1940	Z. ang. Chem. 53, 72
3:4'-Dimethyl- biphenyl	$C_{14}H_{14}$	289	14–15	<i>Kruber</i>	1932	Ber. 65, 1382
4:4'-Dimethyl- biphenyl	$C_{14}H_{14}$	292	121	<i>Kruber</i>	1932	Ber. 65, 1382
β -Naphthol	$C_{10}H_8O$	294	123	<i>K. E. Schulze</i>	1884	Ann. 227, 143
Fluorene	$C_{13}H_{10}$	295	115	<i>Berthelot</i>	1867	Cpt. rend. 65, 465
4:5-Benzoinan	$C_{13}H_{12}$	295	—	<i>Kruber</i>	1932	Ber. 65, 1382
α -Naphthonitrile	$C_{11}H_7N$	297	34	<i>Kruber</i>	1932	Ber. 65, 1382
1-Methylbiphen- ylene oxide	$C_{13}H_{10}O$	298	45	<i>Kruber</i>	1932	Ber. 65, 1382
β -Naphthonitrile	$C_{11}H_7N$	304	67	<i>Kruber</i>	1932	Ber. 65, 1382
2-Methylbiphen- ylene oxide	$C_{13}H_{10}O$	304	66	<i>Kruber, Marx</i>	1938	Ber. 71, 2473
β -Naphthyl- amine	$C_{10}H_9N$	305	113	<i>Kruber</i>	1940	Z. ang. Chem. 53, 72
3-Methylbiphen- ylene oxide	$C_{13}H_{10}O$	305	44	<i>Kruber, Lauenstein</i>	1941	Ber. 74, 1693
2-Methyl- fluorene	$C_{14}H_{12}$	317 319	104	<i>Kruber</i>	1932	Ber. 65, 1382
3 Methyl- fluorene	$C_{14}H_{12}$	318	85	<i>Kruber</i>	1932	Ber. 65, 1382
4-Hydroxy- biphenyl	$C_{12}H_{10}O$	319	163	<i>Kruber</i>	1936	Ber. 69, 107
Biphenylene sulphide	$C_{12}H_8S$	332	97	<i>Kruber</i>	1920	Ber. 53, 1565
Phenanthrene	$C_{14}H_{10}$	340	99	<i>Fittig, Ostermayer</i>	1873	Ann. 166, 361
2-Hydroxy- biphenylene oxide	$C_{12}H_8O_2$	348	143	<i>Kruber</i>	1936	Ber. 69, 107
Phenanthridine	$C_{13}H_9N$	349	106	<i>Sielisch, Sandke</i>	1933	Ber. 66, 433
3-Methyl- phenanthrene	$C_{15}H_{12}$	350	65	<i>Kruber, Marx</i>	1938	Ber. 71, 2473
2-Hydroxyfluor- ene	$C_{12}H_{10}O$	ca. 352	—	<i>Kruber</i>	1936	Ber. 69, 107
Phenanthrylene- methane-(4:5)	$C_{15}H_{10}$	353	116	<i>Kruber</i>	1934	Ber. 67, 1000
1-Methyl- phenanthrene	$C_{15}H_{12}$	354	119	<i>Kruber, Marx</i>	1938	Ber. 71, 2473
9-Methyl- phenanthrene	$C_{15}H_{12}$	354	92	<i>Kruber, Marx</i>	1938	Ber. 71, 2473
Carbazole	$C_{12}H_9N$	355	238	<i>Graebe, Glaser</i>	1872	Ann. 163, 343
2-Phenyl- naphthalene	$C_{16}H_{12}$	357	103	<i>Kruber, Marx</i>	1938	Ber. 71, 2473
Anthracene	$C_{14}H_{10}$	360	213	<i>Dumas, Laurent</i>	1833	Ann. 5, 10
Acridine	$C_{13}H_9N$	over 360	107	<i>Graebe, Caro</i>	1871	Ann. 158, 265

Name	Formula	B.p. 760 mm °C	M.p. °C	Discoverer	Year	Literature
β -Methyl- anthracene	$C_{15}H_{12}$	over 360	190	<i>Japp, G. Schultz</i>	1877	Ber. 10, 1049
Fluoranthene	$C_{15}H_{10}$	over 360	109	<i>Fittig, Gebhard</i>	1878	Ann. 193, 142
1:2:3:4-Tetra- hydrofluor- anthene	$C_{15}H_{14}$	362	76	<i>O. Kruber</i>	1934	Ber. 67, 1000
Pyrene	$C_{16}H_{10}$	over 360	148	<i>Graebe</i>	1871	Ann. 158, 285
2-Methyl- carbazole	$C_{13}H_{11}N$	363	259	<i>Kruber, Marx</i>	1938	Ber. 71, 2478
3-Methyl- carbazole	$C_{13}H_{11}N$	365	207	<i>Kruber, Marx</i>	1938	Ber. 71, 2478
β,β -Naphthylene- phenylene oxide (Brazan)	$C_{16}H_{10}O$	393	205	<i>Winterstein, Schön, Vetter</i>	1934	Z. physiol. Ch. 230, 158
2-Phenanthrol	$C_{14}H_{10}O$	395	169	<i>Kruber</i>	1936	Ber. 69, 246
1:9-Benzo- xanthene	$C_{16}H_{10}O$	395	100	<i>Kruber</i>	1937	Ber. 70, 1570
1:2-Benzo- fluorene	$C_{17}H_{12}$	400	189	<i>Kruber</i>	1937	Ber. 70, 1570
2:3-Benzo- fluorene	$C_{17}H_{12}$	402	208	<i>Kruber</i>	1937	Ber. 70, 1570
1:2-Benzo- naphthacene	$C_{22}H_{14}$	over 425	—	<i>Winterstein and Schön</i>	1934	Naturw. 22, 237 (1934)
Naphtho-2':3'- 1:2-anthracene	$C_{22}H_{14}$	over 425	—	<i>Winterstein and Schön</i>	1934	Naturw. 22, 237 (1934)
3:4-Benzo- acridine	$C_{17}H_{11}N$	434	107	<i>Kruber</i>	1940	Z. ang. Chem. 53, 74
Phenanthridone	$C_{13}H_9ON$	435	286	<i>Kruber</i>	1939	Ber. 72, 771
1:2-Benzo- acridine	$C_{17}H_{11}N$	437	131	<i>Kruber</i>	1941	Ber. 74, 1688
1:2-Benzo- carbazole	$C_{16}H_{11}N$	440	235	<i>Winterstein, Schön, Vetter</i>	1934	Z. physiol. Ch. 230, 158
Triphenylene	$C_{18}H_{12}$	440	197	<i>Kaffer</i>	1935	Ber. 68, 1812
Dibenzo- thionaphthene	$C_{16}H_{10}S$	440	160	<i>Kruber, Rappen</i>	1940	Ber. 73, 1184
3:4-Benzpyrene	$C_{20}H_{12}$	over 440	176	<i>Cook and co-workers</i>	1933	Soc. 1933, 395
Perylene	$C_{20}H_{12}$	over 440	266	<i>Cook and co-workers</i>	1933	Soc. 1933, 395
1:2-Benz- anthracene	$C_{18}H_{12}$	over 440	176	<i>Cook and co-workers</i>	1933	Soc. 1933, 395
peri-Naphtho- xanthene	$C_{18}H_{10}O$	446	177	<i>Kruber</i>	1941	Ber. 74, 1688
Chrysene	$C_{18}H_{12}$	448	250	<i>Laurent</i>	1837	Ann. chim. phys. (2) 66, 136
Phenylnaphthyl- carbazole	$C_{16}H_{11}N$	over 450	330	<i>Brunck, Vischer, Graebe</i>	1879	Ber. 12, 341
1:2-Benzpyrene	$C_{20}H_{12}$	over 450	177	<i>Cook, Hewett, Hieger</i>	1933	Soc. 1933, 395
4:5-Benzpyrene	$C_{20}H_{12}$	over 450	179	<i>Cook, Hewett, Hieger</i>	1933	Soc. 1933, 395
Naphthacene	$C_{18}H_{12}$	over 450	377	<i>Winterstein and Schön</i>	1934	Naturw. 22, 237 (1934)
3:4-Benzo- carbazole	$C_{16}H_{11}N$	452	137	<i>Kruber</i>	1941	Ber. 74, 1688
9:10-Dihydro- naphthacene	$C_{18}H_{14}$	over 450	?	<i>Berlin and Horn</i>		C. 1940, II, 3104
9:10-Dihydro- anthracene	$C_{14}H_{12}$	over 450		<i>Berlin and Horn</i>		C. 1940, II, 3104

III. Number of structural isomerides of some aliphatic compounds

Name	Formula	Number of isomerides (Total number of C atoms = n)							
		n=1	2	3	4	5	6	7	8
Paraffins	C_nH_{2n+2}	1	1	1	2	3	5	9	18
Olefins	C_nH_{2n}		1	1	3	5	13	27	66
Acetylene homologues	C_nH_{2n-2}		1	1	2	3	7	14	32
Primary alcohols	$C_nH_{2n+1}OH$	1	1	1	2	4	8	17	39
Secondary alcohols				1	1	3	6	15	33
Tertiary alcohols					1	1	3	7	17
Alcohols together ¹		1	1	2	4	8	17	39	89
Ethers	$C_nH_{2n+2}O$		1	1	3	6	15	33	82
Glycols (except gem. glycols)	$C_nH_{2n}(OH)_2$		1	2	6	14	38	97	260
Primary amines	$C_nH_{2n+3}N$	1	1	2	4	8	17	39	89
Secondary amines			1	1	3	6	15	33	82
Tertiary amines				1	1	3	7	17	40
Amines together		1	2	4	8	17	39	89	211
Tetraalkylammonium salts ²	$C_nH_{2n+4}NX$				1	1	3	7	18
Carboxylic acids ³	$C_{n-1}H_{2n-1}COOH$	1	1	1	2	4	8	17	39
Esters of carboxylic acids	$C_nH_{2n}O_2$		1	2	4	9	20	45	105
Ketones	$C_{n-1}H_{2n}CO$			1	1	3	6	15	33
Aminocarboxylic acids ⁴	$C_{n-1}H_{2n-2}NH_2COOH$	(1)	1	2	5	12	31	80	210
Dicarboxylic acids ⁵	$C_{n-2}H_{2n-4}(COOH)_2$		1	1	2	4	9	21	52

¹ Monohydric saturated alcohols. The number of isomerides is the same if other monovalent radicals (e.g. Cl, Br, I, SH) are substituted for OH.
² The number of isomerides is the same for lead tetraalkyls, etc.
³ Monobasic saturated carboxylic acids. The numbers of isomerides are also the same for the corresponding aldehydes.
⁴ The numbers of isomerides are the same for hydroxy- and halogen-substituted carboxylic acids.
⁵ Dibasic saturated carboxylic acids.

IV. Numbers of isomerides of paraffins and alcohols, with and without stereoisomerides

(The numbers, which **also** take stereoisomerides into account, are printed in **heavy type**)

n =	1	2	3	4	5	6	7	8	9	10	20
C_nH_{2n+2}	1	1	1	2	3	5	9	18	35	75	366,319
$C_nH_{2n+1}OH$	1	1	1	2	3	5	11	24	55	136	3,395,964
	1	1	2	4	8	17	39	89	211	507	5,622,109
	1	1	2	5	11	28	74	199	551	1,553	82,299,275

V. Number of structural isomerides of cyclic hydrocarbons

Name	Formula	Number of isomerides (Total number of C-atoms = n)					
		n = 3	4	5	6	7	8
Cyclopropane homologues	C_nH_{2n}	1	1	3	6	15	33
Cyclobutane homologues			1	1	4	8	24
Cyclopentane homologues				1	1	4	9
Cyclohexane homologues					1	1	5
Cycloheptane homologues						1	1
Cyclooctane							1
Cycloparaffins together		1	2	5	12	29	73
		Number of carbon atoms outside the aromatic nucleus = n					
		n = 1	2	3	4	5	6
Benzene homologues	$C_6H_6C_nH_{2n}$	1	4	8	22	51	136
Naphthalene homologues	$C_{10}H_8C_nH_{2n}$	2	12	32	110	310	920
Anthracene homologues	$C_{14}H_{10}C_nH_{2n}$	3	18	61	225	716	2,272
Phenanthrene homologues	$C_{14}H_{10}C_nH_{2n}$	5	30	115	425	1,396	4,440

VI. Number of structural isomerides of the substitution products of some cyclic parent compounds

(X, Y, Z are monovalent radicals, different from each other, which each replace one hydrogen atom of the original compound)

	Benzene	Naphthalene	Anthracene	Phenanthrene	Thiophen
X	1	2	3	5	2
X_2	3	10	15	25	4
XY	3	14	23	45	6
X_3	3	14	32	60	2
X_2Y	6	42	92	180	6
XYZ	10	84	180	360	12
X_4	3	22	60	110	1
X_3Y	6	70	212	420	2
X_2Y_2	11	114	330	640	4
X_2YZ	16	210	632	1,260	6

Literature for the above tables III-VI:

H. R. Henze and C. M. Blair, J. Am. Ch. Soc. 53, 3042, 3077; 54, 1098, 1538; 55, 252, 680; 56, 157. — A. C. Lunn and J. K. Senior, J. phys. Chem. 33, 1027. — G. Pólya, Z. f. Kristallographie (A) 93, 415.

VII. World production of coal, 1938¹

(in millions of tons)

Europe (including U.S.S.R.)	Asia, Africa, and Australia	America
Great Britain (202.9) 231.8	Japan (28.7) 46.0	U.S.A. (613.3) . . . 352.3
Germany (72.5) . . . 186.2	India (27.4) 25.6	Canada (14.4) . . . 9.8
U.S.S.R. (—) 132.9	China (5.0) —	Other countries . . . 3.0
France (47.3) 46.5	S. Africa (23.0) . . 18.6	
Poland (59.1) 38.1	Australia (14.7) . . 12.2	
Belgium (24.4) 29.6	Other countries . . . 42.0	
Czechoslovakia (16.3) 13.8		
Other countries 21.1		
Total Europe 700.0	Total Asia, Africa, and Australia . . . 144.4	Total America . . . 365.1

World production in 1938 about 1,225.0 million tons.

¹ The figures given in brackets after the names of the countries are for the year 1947. They are taken from "Iron & Coal Trades Review" 155, 1124 (1947); 157, 270 (1948). They represent metric tons.

VIII. Estimate of the coal reserves of the world (1936)

(in milliards of tons)

	Coal and An- thracite	Lignite		Coal and An- thracite	Lignite
Germany	289	57	China	217	0.6
England and Ireland .	200	—	Russia (Asiatic) . . .	1,007	9.8
Poland	138	17	India	76	2.6
Russia (European) . .	75	6	Indo-china	20	—
France	17	1.6	Japan	17	0.8
Belgium	11	—	Sou h Africa	66	—
Spitzbergen	9	—	U.S.A.	1,975	1,863
Spain	8	0.8	Canada	243	860
Czechoslovakia . . .	28	12	Columbia	27	—
Holland	4.4	—	Australia	133	33

IX. Increase in the production of mineral oil

(figures in 1000 tons)

	1860	1880	1900	1913	1937	1940	1947 ¹
U.S.A.	69	3,601	8,716	34,037	179,000	188,000	266,495
Russia		411	10,382	8,608	28,184	30,987	27,100
Venezuela					27,771	28,000	63,364
Persia				254	10,330	10,500	20,500
Dutch East Indies			411	1,492	7,262	8,400	1,119
Rumania	1	16	250	1,886	7,457	5,810	3,929
Galicia		32	326	1,071	540	560	—
Mexico				3,520	6,835	5,800	8,088
British India . . .			148	1,086	1,456	1,400	257
Germany			49	117	486	660	577
Japan			119	266	368	377	182
Canada		48	125	31	398	1,200	1,020
Peru				284	2,428	1,800	1,794
Sarawak					793	1,000	1,826
Argentina					2,322	2,900	3,133
Trinidad					2,262	2,900	3,018
Colombia					2,932	3,900	3,542
Iraq					4,337	3,600	4,721
Bahrein					1,061	1,000	1,287
Saudi-Arabia . . .							12,208
Other countries . .		4	40	181	703	2,591	6,285
Total:	70	4,112	20,566	52,833	286,925	301,385	430,445

¹ Data by courtesy of the N.V. Bataafsche Petroleum Maatschappij, The Hague.

X. Estimate of world sugar production

(figures in 1000 tons)

Beet sugar	1922/23	1936/37	1940/41	Cane sugar	1922/23	1936/37	1940/41
Germany	1,455	1,626	}2,416	Brit. East Indies	3,093	3,960	3,540
Austria	114	258		Cuba	3,704	2,880	2,400
Russia	233	1,999		Java	1,779	1,415	1,758
U.S.A.	658	1,183	1,608	Brazil	761	959	1,192
Italy	300	310	547	Japan & Formosa	425	1,113	982
Czechoslovakia .	736	634	526	Philippines . .	431	947	937
England	—	530	493	Hawaii	487	862	803
France	495	796	436	Porto Rico . . .	817	344	800
Sweden	72	269	280	Australia	311	748	770
Holland	249	220	269	Argentina	216	433	541
Belgium	265	219	232	Union of S. Africa	—	405	520
Denmark	89	203	213	Peru	319	410	462
Spain	159	226	151	San Domingo . .	187	429	380
Poland	304	412	98	Mexico	—	295	335
Other countries	134	548	763	Mauritius	231	300	316
				U.S.A.	267	374	282
				Other countries	930	1,603	1,622
	5,263	9,433	10,340		13,485	17,950	17,640

XI. Comparison of the world production of beet sugar and cane sugar during the years 1893-1939
(figures in 1000 tons)

	1895-96	1910-11	1920-21	1934-35	1938-39
Beet sugar. . . .	4,248	8,588	4,647	8,870	9,700
Cane sugar	2,839	8,422	10,944	14,100	17,390

XII. Relative sweetness of various organic substances¹
(referred to cane sugar as 1)

Substance	Formula	Sweetness
Cane sugar.	$C_{12}H_{22}O_{11}$	1
Lactose	$C_{12}H_{22}O_{11}$	0.27
Dulcitol	$C_6H_{14}O_6$	0.41
Mannitol	$C_6H_{14}O_6$	0.45
Sorbitol	$C_6H_{14}O_6$	0.48
Glycerol	$C_3H_8O_3$	0.48
Ethylene glycol	$C_2H_6O_2$	0.49
D-Glucose	$C_6H_{12}O_6$	0.5-0.6
Maltose	$C_{12}H_{22}O_{11}$	0.6
Invert sugar		0.8-0.9
Fructose	$C_6H_{12}O_6$	1.0-1.5
<i>p</i> -Anisylurea	$CH_3OC_6H_4NHCONH_2$	18
Chloroform	$CHCl_3$	40
<i>p</i> -Methylsaccharin	$CH_3C_6H_3COSO_2NH$	200
Dulcine	$C_2H_5OC_6H_4NHCONH_2$	70-350
6-Chlorosaccharin	$ClC_6H_3COSO_2NH$	100-350
<i>n</i> -Hexyl-chloromalonamide	$n-C_6H_{13}CCl(CONH_2)_2$	300
Saccharin	$C_6H_4COSO_2NH$	200-700
1-Ethoxy-2-amino-4-nitrobenzene.	$C_6H_3(OC_2H_5)(NH_2)(NO_2)$	950
Perillaldehyde <i>anti</i> -aldoxime (Peryllartine).	$C_6H_8C(CH_3)CH_2CHNOH$	2,000
1- <i>n</i> -Propoxy-2-amino-4-nitrobenzene	$C_6H_3(OC_3H_7)(NH_2)(NO_2)$	4,100

Since the sweetness of a substance depends on the concentration of the solution, and not all compounds were tested under the same conditions of concentration, the figures given by various observers vary within certain limits.

¹ According to C. F. Walton, International Critical Tables, Vol. I, New York, 1926.

XIII. Classification of odours
(based on Linné-Zwaardemaker)

Type of smell	Examples
1. <i>Ethereal smell</i>	Ethyl acetate, ethyl alcohol, acetone, amyl acetate
2. <i>Aromatic smell</i>	
(a) Almond	Nitrobenzene, benzaldehyde, benzonitrile
(b) Camphor.	Camphor, thymol, carvacrol, safrole, eugenol
(c) Lemon	Citral, linalool acetate
3. <i>Balsam smell</i>	
(a) Flower.	Methyl anthranilate, terpineol, citronellol
(b) Lily	Heliotropin, styrone
(c) Vanilla	Vanillin, anisaldehyde
4. <i>Musk smell</i>	Trinitroisobutyltoluene, ambrette musk, muscone
5. <i>Garlic smell</i>	Ethyl sulphide
6. <i>Cacodylic smell</i>	Cacodyl, trimethylamine
7. <i>Empyreumatic smell</i>	Isobutyl alcohol, aniline, cumidine, benzene, cresol, guaiacol
8. <i>Rancid smell</i>	Valeric acid, caproic acid, methyl heptyl ketone, methyl nonyl ketone
9. <i>Narcotic smell</i>	Pyridine, pulegone
10. <i>Repulsive smell</i>	Skatole, indole

XIV. Minimal concentrations of some perfumes at which they can still be detected by their smell¹

	No. of molecules per c.c. which can still be detected		No. of molecules per c.c. which can still be detected
Ionone.	16 × 10 ⁵	Heliotropin	40 × 10 ⁷
Ethyl disulphide. . .	15 × 10 ⁶	Thymol	15 × 10 ⁸
Skatole.	16 × 10 ⁶	Pyridine	31 × 10 ⁸
Vanillin	20 × 10 ⁶	Safrole	48 × 10 ⁸
Toluene musk. . . .	21 × 10 ⁶	Bornyl acetate. . . .	14 × 10 ⁹
Coumarin	33 × 10 ⁶	Methyl acetate	16 × 10 ⁹
Citral	40 × 10 ⁶	Carvone	22 × 10 ⁹
Butyric acid.	69 × 10 ⁶	Trimethylamine	22 × 10 ¹⁰
Vanillin	72 × 10 ⁶	Phenol	26 × 10 ¹⁰
Guaiacol	20 × 10 ⁷	Menthol	26 × 10 ¹⁰
Nitrobenzene	32 × 10 ⁷	Ethyl alcohol	24 × 10 ¹²

¹ Chiefly according to Zwaardemaker. These values are, of course, not very accurate, and give only a rough idea of the order of magnitude.

XV. The most important poisonous compounds occurring in industry (principal and by-products)¹

Principal products		
Halogens, Cl_2 , Br_2 , I_2 Halogen hydracids Sulphur dioxide, SO_2 Hydrogen sulphide, H_2S Sulphur monochloride, S_2Cl_2 Nitrogen oxides (NO_2 , N_2O_4) Phosphorus chlorides, PCl_3 , PCl_5 Prussic acid, HCN Phosgene, COCl_2 Formaldehyde, CH_2O Acetone, CH_3COCH_3 Methyl ethyl ketone, $\text{CH}_3\text{COC}_2\text{H}_5$ Ethyl chlorocarbonate Chloroacetone, $\text{CH}_2\text{ClCOCH}_3$	Methyl alcohol, CH_3OH Propyl alcohol, $\text{C}_3\text{H}_7\text{OH}$ Butyl alcohol, $\text{C}_4\text{H}_9\text{OH}$ Petrol Carbon tetrachloride, CCl_4 Chloroform, CHCl_3 Tetrachloroethane, $\text{CHCl}_2 \cdot \text{CHCl}_2$ Trichloroethylene, $\text{CCl}_2 = \text{CHCl}$ Methyl halides, CH_3X ($\text{X} = \text{Cl}, \text{Br}, \text{I}$) Ethyl halides, $\text{C}_2\text{H}_5\text{X}$ ($\text{X} = \text{Cl}, \text{Br}, \text{I}$) Dimethyl sulphate, $(\text{CH}_3)_2\text{SO}_4$	Diazomethane, CH_2N_2 Hydrazoic acid, HN_3 Benzene, C_6H_6 Phenol, $\text{C}_6\text{H}_5\text{OH}$ Toluenesulphonyl chloride, $\text{CH}_3\text{C}_6\text{H}_4\text{SO}_2\text{Cl}$ Aniline, $\text{C}_6\text{H}_5\text{NH}_2$ <i>p</i> -Aminophenol, $\text{HOC}_6\text{H}_4\text{NH}_2$ <i>o</i> -Phenetidine, $\text{C}_6\text{H}_4(\text{NH}_2)^1(\text{OC}_2\text{H}_5)^2$ Nitrobenzene, $\text{C}_6\text{H}_5\text{NO}_2$ <i>m</i> -Dinitrobenzene, $\text{C}_6\text{H}_4(\text{NO}_2)^1(\text{NO}_2)^3$ <i>o</i> -Chloronitrobenzene, $\text{C}_6\text{H}_4(\text{NO}_2)^1(\text{Cl})^2$
By-products		
Hydrogen sulphide Nitric oxides Sulphur dioxide, SO_2 Arsine, AsH_3 Phosphine, PH_3 Phosphorus oxychloride, POCl_3	Silicofluoroform, SiF_3H Silicon tetrafluoride, SiF_4 Silicomethane, SiH_4 Dichloroacetylene, $\text{CCl} \cdot \text{CCl}$ Acrolein, $\text{CH}_2 : \text{CH} \cdot \text{CHO}$ Tetranitromethane, $\text{C}(\text{NO}_2)_4$	Dichloro-dinitromethane, $\text{CCl}_2(\text{NO}_2)_2$ Carbon tetrafluoride, CF_4 Dimethylmercury, $(\text{CH}_3)_2\text{Hg}$ Diazomethane, CH_2N_2

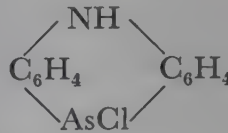
¹ According to A. Zangger.

XVI. The best-known poisonous substances used in warfare¹

Inorganic compounds

Chlorine, Cl ₂ Bromine, Br ₂ Hydrogen chloride, HCl Hydrogen bromide, HBr Nitrogen dioxide, NO ₂ Nitrosyl chloride, NOCl Nitrosyl bromide, NOBr Phosphine, PH ₃	Arsine, AsH ₃ Hydrogen sulphide, H ₂ S Sulphur dioxide, SO ₂ Sulphur trioxide, SO ₃ Thionyl chloride, SOCl ₂ Thionyl fluoride, SOF ₂ Sulphuryl chloride, SO ₂ Cl ₂	Chlorosulphonic acid, ClSO ₃ H Arsenic trichloride, AsCl ₃ Stannic chloride, SnCl ₄ Silicon tetrachloride, SiCl ₄ Titanium tetrachloride, TiCl ₄
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Organic compounds

*Phosgene, COCl ₂ *Dimethyl sulphate, SO ₂ (OCH ₃) ₂ Methyl chlorosulphonate, ClSO ₃ CH ₃ Ethyl chlorosulphonate, ClSO ₃ C ₂ H ₅ Methyl bromoacetate, CH ₂ BrCO ₂ CH ₃ Ethyl iodoacetate, CH ₂ ICO ₂ C ₂ H ₅ Ethyl chloroformate, ClCO ₂ C ₂ H ₅ Chlorinated formic acid and methyl chloroformate, ClCO ₂ CH ₂ Cl, ClCO ₂ CHCl ₂ , *ClCO ₂ CCl ₃ *Di-(chloromethyl) ether, ClCH ₂ OCH ₂ Cl Di-(bromomethyl) ether, BrCH ₂ OCH ₂ Br *Di-(chloroethyl) sulphide, ClC ₂ H ₄ SC ₂ H ₄ Cl *Chloracetone, CH ₃ COCH ₂ Cl Bromacetone, CH ₃ COCH ₂ Br Iodoacetone, CH ₃ COCH ₂ I	Bromomethyl ethyl ketone, CH ₂ BrCOC ₂ H ₅ *Chloracetophenone, C ₆ H ₅ COCH ₂ Cl Benzyl chloride, C ₆ H ₅ CH ₂ Cl *Benzyl bromide, C ₆ H ₅ CH ₂ Br Benzyl iodide, C ₆ H ₅ CH ₂ I *Xylol bromide, C ₆ H ₄ (CH ₃)CH ₂ Br Prussic acid, HCN Cyanogen chloride, CNCl *Cyanogen bromide, CNBr Methyl cyanoformate, CN·CO ₂ CH ₃ Phenylcarbylamine di- chloride, C ₆ H ₅ ·N:CCl ₂ *Chloropicrin, CCl ₃ NO ₂ *Methyldichlorarsine, CH ₃ AsCl ₂ *Ethyldichlorarsine, C ₂ H ₅ AsCl ₂ Phenyldichlorarsine, C ₆ H ₅ AsCl ₂ *Diphenylchlorarsine, (C ₆ H ₅) ₂ AsCl Diphenylcyanarsine, (C ₆ H ₅) ₂ AsCN	Chlorovinylchlorarsine, CHCl:CH·AsCl ₂ Di-(chlorovinyl)-chlorarsine, (CHCl:CH) ₂ AsCl Tri-(chlorovinyl)-arsine, (CHCl:CH) ₃ As Diphenylaminechlorarsine, <div style="text-align: center;">  </div> Carbon monoxide, CO Acrolein, CH ₂ :CHCHO Butyl mercaptans, C ₄ H ₉ SH Perchloromethyl mercaptan, CCl ₃ SH Methyl trithiocarbonate, CS(SCH ₃) ₂ Allyl mustard oil, CH ₃ NCS Diphenylchlorostibine, (C ₆ H ₅) ₂ SbCl Diphenylcyanostibine, (C ₆ H ₅) ₂ SbCN
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¹ According to Julius Meyer.

* Particularly often used.

Many poison gases are known by special names, e.g.:

Diphenylchlorarsine:	Clark I (G.), DA (Br. and Am.)
Diphenylcyanarsine:	Clark II (G.), DC (Br.), CDA (Am.)
Diphenylaminechlorarsine:	Adamsite (Am.), DM (Br. and Am.)
Chlorvinylchlorarsine:	Lewisite (Br.), M-I (Am.)
Ethylchlorarsine:	Dick (G.), ED (Am.)
Di-(chloroethyl) sulphide:	Lost (G.), Yperite (Fr.), Mustard gas (Br. and Am.)
	BB (Br.), HS (Am.)
Trichloromethyl chloroformate:	Perstoff (G.), Surpalite (Fr.), Diphosgene (Br.)
Chloracetophenone:	CAP (Br.), CN (Am.)
Bromacetone:	B-stoff (G.), Martonite (Fr.), BA (Br. and Am.)
Xylyl bromide:	T-stoff (G.)
Carbonyl chloride (phosgene):	D-stoff (G.), Collongite (Fr.), CG (Br. and Am.)
Bromobenzyl cyanide:	Camite (Fr.), BBC (Br.), CA (Am.)
Benzyl bromide:	T-stoff (G.), Cyclite (Fr.)
Ethyl chlorosulphonate:	Sulvanite (Fr.)
Chloropicrin:	Klop (G.), Aquinite (Fr.), Vomiting gas (Br.), PS and NC (Br. and Am.)
Acrolein:	Papite (Fr.)
Cyanogen bromide:	Campillit (It.), Ce (Au.), CB (Br.)

Abbreviations are as follows: G. = German, Br. = British, Am. = American, Fr. = French, It. = Italian, and Au. = Austrian.

XVII. Table showing the effects of corrosive and poisonous gases and vapours, in milligrams per litre¹

Name	Im- mediate death	Fatal in $\frac{1}{2}$ –1 hr. or later	Producing dan- gerous effects in $\frac{1}{2}$ –1 hr.	Tolerable for $\frac{1}{2}$ – 1 hr. without im- mediate or late consequences
Chlorine	2.5	0.10–0.15	0.04–0.06	0.01
Bromine	3.5	0.22	0.04–0.06	0.022
Hydrogen chloride.	—	1.84–2.60	1.50–2.00	0.06–0.13
Sulphur dioxide.	—	1.40–1.70	0.40–0.50	0.17
Ammonia	—	1.50–2.70	1.50–2.50	0.18
Hydrogen sulphide	1.2–2.8	0.60–0.84	0.50–0.70	0.24–0.36
Nitrous fumes.	}	0.60–1.00	—	0.20–0.40
Nitric acid				
Nitrous acid				
Prussic acid.	0.3	0.12–0.15	0.12–0.15	0.05–0.06
Arsine	5.0	0.05	0.02	0.02
Phosphine	—	0.56–0.84	0.40–0.60	0.14–0.26
Osmium tetroxide OsO ₄	—	—	—	0.001
Carbon dioxide	—	90–120	60–80	60–70
Carbon monoxide	}	2–3	2–3	0.50–1.00
Fumes 0.1–0.5%				
Coal gas 5–10%				
Producer gas 24%				
Explosive gas 30–60%				
Phosgene.	—	0.02–0.10	0.05	—
Petrol	—	30–40	25–30	10–20
Chloroform.	—	200	—	30–40
Carbon tetrachloride.	—	400–500	150–200	60–80
Carbon disulphide.	—	15	10–12	3–5
Aniline, Toluidine.	—	—	—	0.5
Nitrobenzene	—	—	—	1.0–1.5

¹ According to Lehmann, Hess, and Zangger.

**XVIII. Limits of tolerance of human beings
towards some poisonous substances**

(Content of liquid or solid substance in 1 m³ of air)

1. Diphenylarsine cyanide. . .	0.25 mg	20. Methyl bromoacetate . .	45 cmm
2. Diphenylarsine chloride. .	1—2 „	21. Ethylsulphuric acid	
3. Paranitrophenylarsine		chloride	50 „
dichloride	2.5 „	22. Cyanogen chloride . . .	> 50 „
4. Naphthylarsine dichlo-		23. Chloropicrin	60 „
ride	> 5 „	24. Ethyl iodoacetate . . .	60 „
5. Ethylarsine oxide	5—7 „	25. Acrolein	70 „
6. Ethylarsine dichloride . .	5—10 cmm	26. Chlorinated methyl	
7. Methylarsine oxide . . .	5 „	formate	75 „
8. Cacodyl cyanide	10 „	27. Ethyl bromoacetate . . .	80 „
9. Phenylarsine dichloride .	10 „	28. Benzoyl chloride	85 „
10. Benzyl iodide.	15 „	29. Cyanogen bromide	85 „
11. Xyllyl bromide	15 „	30. Allyl mustard oil	90 „
12. Cacodyl chloride	20 „	31. Chloroacetone	> 100 „
13. Methylarsine dichloride .	25 „	32. Iodoacetone	> 100 „
14. Formaldehyde	25 „	33. Arsenic trichloride. . . .	> 100 „
15. Cacodyl oxide	30 „	34. Chlorine.	> 150 „
16. Bromoacetone	30 „	35. Ammonia	500 „
17. Isocyanophenyl chloride .	30 „		
18. Methylsulphuric acid			
chloride	30—40 „		
19. Benzyl bromide.	30—40 „		

XIX. World production and use of the more important textiles¹

	1913 tons	1927 tons	1936 tons	1938 tons
Wool	1,388,090	1,603,100	1,747,000	1,780,000
Cotton	ca. 5,000,000	5,195,000	6,870,000	6,240,000
Natural silk	33,778	54,000	54,000	54,000
Artificial silk	11,500	140,250	461,600	451,000
Staple rayon	—	—	133,600	445,570

¹ Taken from the Annual Statistical Review of League of Nations.

**XX. Amount of cotton, natural silk, and artificial silk produced
by the most important producing countries**

	1938 Cotton tons	1937 Natural silk tons	1938 Artificial silk tons
Egypt	330,000	—	—
Belgium	—	—	5,100
British India	929,000	63	—
China	?	4,905	—
Germany	—	—	65,000
England	—	—	48,285
France	—	50	28,000
Holland	—	—	9,000
Japan	—	41,875	96,500
Italy	—	3,166	45,996
Switzerland	—	—	5,500
Turkey	66,000	180	—
U.S.A.	2,590,000	—	116,990
Russia	835,000	ca. 1,680	7,000
Brazil	407,000	—	5,000
Remaining countries	103,000	ca. 2,181	18,829

XXI. The best-known artificial materials

Trade name	Chemical composition	Country of origin	Application
Bakelite	Phenol-formaldehyde	U.S.A., Germ., Eng., Italy	Thermally hardened mass for moulded articles for all kinds of purposes.
Lignofol	Phenol-formaldehyde with wood veneer	Germany	Machine constructions. Construction elements in general.
Haveg	Phenol-formaldehyde-asbestos	Germany	Acid-resisting lining or construction material.
Pollopas	Urea-formaldehyde	Germ., Engl., France	Light shaded moulded articles.
Beetle	" "	U.S.A.	Idem.
Ultrapas	Melamine-formaldehyde	Germany	Idem.
Cibanit	Aniline-formaldehyde	Switzerland	Insulating material preventing creeping current.
Iganil	" "	Germany	Idem.
Igamid	Superpolyamide	Germany	Injection moulding.
Nylon	" "	U.S.A.	Artificial silk for stockings, brushes, fishing-nets.
Perlon	" "	Germany	Idem.
Thiokol	Polyethylene polysulfide	U.S.A.	Substitute for rubber; resistant to oil, petrol, and benzene.
Perduren	" "	Germany	
Stamikol	" "	Holland	
Vinidur	Polyvinyl chloride	Germany	Tubes, rods, blocks, foils. Chemically resistant covers and linings. Can be heat-welded.
P.C.fibre	Chlorinated Polyvinyl chlorides	Germany	Thread; fishing-nets; filter cloth in the chemical industry.
Vinyarm	Polyvinyl alcohol	U.S.A.	Rubbery linings resistant to benzene.
Resistoflex		U.S.A.	
Acronal	Polyacrylic ester	Germany	Cables, hoses, impregnations.
Plexiglas	Polymethacrylic ester	Germany	"Organic glass". Panes for aircrafts.
Diacon	" "	U.S.A.	Protheses.
Paladon	" "	Germany	Foils for high-frequency insulations.
Styroflex	Polystyrene	Germany	Injection moulding. Especially for electrical purposes.
Trolitul	" "	Germany	Rubbery linings, chemically resistant.
Oppanol	Polyisobutylene	Germany	Tubes, rods, foils for chemically resistant linings. Can be heat-welded.
Mipolam	Mixed polymer from vinyl alcohol and vinyl acetate	Germany	Fibres for garments, etc.
Koroseal	Idem	U.S.A.	Synthetic rubber.
Vinyon	Idem	U.S.A.	Oil-resistant synthetic rubber
SKA; SKB	Polybutadiene	Russia	Synthetic rubber.
Neoprene	Chloroprene	U.S.A.	
Buna S	Mixed polymer from butadiene and styrene	Germany	
Perbunan	Mixed polymer from butadiene and acrylonitrile	Germany	Oil-resistant synthetic rubber.
Ameripol	Mixed polymer from isobutylene and butadiene	U.S.A.	Synthetic rubber.
Tornesit	Chlorinated rubber	Germany	Basis for lacquers.
Pliofilm	HCl-rubber	U.S.A.	Matting material. Waterproof-dressing.
Pliolite	Cyclized rubber	U.S.A.	Basis for lacquers.
Monit	Vulcanized fibre	Germany	Boards, tubes, rods.
Celluloid	Nitrocellulose with camphor	Germany	Boards, moulded articles, etc.
Trolit F	Nitrocellulose with mineral filler	Germany	Extruded profiles (rods, tubes etc.).
Trolit W	Cellulose acetate	Germany	Injection moulding.
Galalith	Casein-formaldehyde	Germany	Flat articles, buttons, extruded profiles.
Lanital	" "	Italy	Milkwool.

XXII. Comparison of properties of some explosives¹

	Max. density (crystal density)	Gas vol. (spec. vol.) at 0°/760 mm l/kg	Heat of explosion Rv cal./kg.	Detona- tion temper- ature	Max. velocity of deto- nation m/sec.	Sensitivity (height from which 2 kg weight is dropped, in cm)
Tetranitromethane-toluene, 86.5/ 13.5 liquid (mixture of max. destructive power)	1.46	659	1,759	5,650°	9,300	6
Nitroglycerine, liquid	1.59	715	1,563	4,830°	8,000	6
Glycol dinitrate (liquid)	1.49	737	1,670	4,800°	8,000	7
<i>Military explosives:</i>						
Nitrogen tetroxide-nitrobenzene, 70/30, liquid (Panclostite) (for aeroplane bombs)	1.38	662	1,777	5,670°	8,000	7
Pentaerythritol tetranitrate (Pen- trite)	1.77	780	1,485	4,540°	8,100	28
Trimethylenetrinitramine (Hex- ogen, T ₄)	1.82	908	1,302	4,110°	8,300	30
Picric acid (Mélinite)	1.76	675	1,000	3,230°	7,200	60
Trinitrotoluene (Trotyl)	1.67	690	950	2,800°	6,800	90
Guncotton (13.3% N)	1.66	865	1,060	3,040°	6,900	20
<i>Industrial explosives:</i>						
Blasting gelatine 92/8 (100% dy- namite)	1.63	711	1,629	4,890°	7,800	15
Gelatine dynamite 65% (dyna- mite-1)	1.55	650	1,330	4,100°	6,500	20
Safety dynamite 25%	1.50	800	1,100	2,900°	5,800	60
Liquid air-soot explosive (72.7% O ₂ + 27.3% C) (Oxyliquit)	0.80	509	2,130	7,100°	4,700	10
Black powder	1.60	280	710	2,400°	400	70
<i>Detonators²:</i>						
Mercuric fulminate	4.42	315	429	4,450°	5,400	2
Lead azide	4.71	308	367	3,450°	5,400	3
Lead trinitroresorcinate	3.10	407	370	2,730°	5,200	4

¹ Based on data by A. Stettbacker.
² The metal component taken as vaporized.

XXIII. Dissociation constants of some important organic bases¹

Substance	Temp.	Dissociation constant, K ²	Substance	Temp.	Dissociation constant, K ²
(Ammonia	18°	1.75 × 10 ⁻³)	Diethylamine.	25°	1.26 × 10 ⁻¹
Aniline	25°	4.60 × 10 ⁻⁸	Dimethylamine.	25°	7.40 × 10 ⁻²
Ethylamine	25°	5.60 × 10 ⁻²	Glycine	25°	2.70 × 10 ⁻¹⁰
Caffeine	40°	4.10 × 10 ⁻¹²	Isoquinoline	15°	3.60 × 10 ⁻⁸
Quinoline	15°	3.2 × 10 ⁻⁸	Methylamine.	25°	5.00 × 10 ⁻²
Quinine	15°	1.08 × 10 ⁻⁴	<i>p</i> -Phenetidine	15°	2.20 × 10 ⁻⁷
2. Stage	15°	3.30 × 10 ⁻⁶	Piperazine	25°	6.40 × 10 ⁻³
Cinchonine	15°	1.4 × 10 ⁻⁴	Piperidine	25°	1.60 × 10 ⁻¹
2. Stage	15°	3.30 × 10 ⁻⁸	Pyridine.	25°	1.4 × 10 ⁻⁷
Cocaine	15°	2.50 × 10 ⁻⁴	Theobromine.	40°	4.80 × 10 ⁻¹²
Codeine	25°	9 × 10 ⁻⁶	Triethylamine	25°	6.40 × 10 ⁻²
Coniine	25°	1.30 × 10 ⁻¹	Trimethylamine	25°	7.40 × 10 ⁻⁸

¹ According to a compilation by I. M. Kolthoff.
² 100 × k

XXIV. Dissociation constants of the most important organic acids *

Substance	Temp.	Dissociation constant, K^1	Substance	Temp.	Dissociation constant, K^1
Acetic acid.	25°	1.86×10^{-5}	Maleic acid	25°	1.0
Benzoic acid	25°	6.86×10^{-5}	2nd stage	18°	5.5×10^{-5}
<i>n</i> -Butyric acid	25°	1.53×10^{-5}	Malic acid.	25°	4.00×10^{-2}
Camphoric acid	25°	2.95×10^{-2}	2nd stage	18°	9.00×10^{-4}
2nd stage		1.05×10^{-3}	Malonic acid.	25°	1.63×10^{-1}
Cinnamic acid	25°	3.68×10^{-3}	2nd stage	18°	8.0×10^{-5}
Citric acid.	25°	8.70×10^{-2}	Oxalic acid	25°	6.5
2nd stage	18°	1.77×10^{-3}	2nd stage	18°	6.1×10^{-3}
3rd stage	18°	3.9×10^{-4}	Phenol	25°	1.30×10^{-8}
Diethylbarbituric acid.	25°	3.70×10^{-6}	Phthalic acid.	25°	1.26×10^{-1}
Formic acid	18°	2.05×10^{-3}	2nd stage	18°	3.9×10^{-4}
Fumaric acid.	18°	9.3×10^{-2}	Picric acid.	25°	1.60×10^{-1}
2nd stage	18°	3.4×10^{-3}	Propionic acid	25°	1.40×10^{-3}
Gallic acid.	25°	4.00×10^{-3}	Saccharin	18°	2.50
Glycine	25°	3.40×10^{-3}	Salicylic acid.	25°	1.06×10^{-1}
Glycolic acid	25°	1.52×10^{-2}	Succinic acid.	25°	6.60×10^{-3}
Hippuric acid	25°	2.38×10^{-2}	2nd stage	18°	2.70×10^{-4}
Hydrocyanic acid.	25°	7.20×10^{-3}	Sulphanilic acid	25°	6.20×10^{-2}
<i>Isobutyric acid</i>	25°	1.48×10^{-3}	Tartaric acid.	25°	9.60×10^{-2}
Lactic acid.	25°	1.55×10^{-2}	2nd stage	18°	2.80×10^{-3}
			Trichloroacetic acid	18°	1.30×10^{-1}
			Valeric acid	25°	1.60×10^{-3}

¹ $100 \times k$

XXV. pH Intervals over which indicators change colour*

Indicator	pH interval	Acid-alkali colour change
Methyl violet	0.1— 1.5	yellow — blue
Methyl violet	1.5— 3.2	blue — violet
Metanil yellow	1.2— 2.3	red — yellow
Thymolsulphophthalein	1.2— 2.8	red — yellow
Tropæolin OO	1.3— 3.2	red — yellow
Benzopurpurin	1.3— 5.0	blue-violet — orange
Dimethyl yellow (= dimethylamino-azobenzene)	2.9— 4.0	red — blue
Methyl orange	3.1— 4.4	red — orange-yellow
Tetrabromophenolsulphophthalein.	3.0— 4.6	yellow — blue
Congo red	3.0— 5.2	blue-violet — red
Sodium alizarin	3.7— 5.2	yellow — violet
Methyl red	4.2— 6.3	red — yellow
Lacmoid	4.4— 6.4	red — blue
<i>p</i> -Nitrophenol	5.0— 7.0	colourless — yellow
Dibromocresolsulphophthalein	5.2— 6.8	yellow — purple
Dibromothymolsulphophthalein	6.0— 7.6	yellow — blue
Neutral red.	6.8— 8.0	red — yellow
Phenolsulphophthalein	6.8— 8.4	yellow — red
Rosolic acid	6.9— 8.0	brown — red
<i>o</i> -Cresolsulphophthalein	7.2— 8.8	yellow — red
Brilliant yellow	7.4— 8.5	yellow — red-brown
α -Naphthophthalein	7.3— 8.7	pink — blue
Tropæolin OOO	7.6— 8.9	brown-yellow — pink
Turmeric.	7.8— 9.2	yellow — red-brown
Thymolsulphone phthalein	8.0— 9.6	yellow — blue
Phenolphthalein.	8.2—10.0	colourless — red
Thymolphthalein	9.3—10.5	colourless — blue
Alizarin yellow	10.1—12.1	yellow — lilac
Tropæolin O.	11.0—13.0	yellow — orange-brown
Alizarin blue S	11.0—13.0	green — blue

* According to a compilation by I. M. Kolthoff.

XXVI. Constants of the normal primary alcohols

	Molecular heat of com- bustion in kg-cals	ΔCH_2^1	Molecular volumes and differences between successive members ²		Association of the alcohols ³
Methyl alcohol	170.9	156.6 kg. cal.		Δ	$n = ^4 3.17$
Ethyl "	327.5				
Propyl "	483.3	155.8 "	92.76 cm ³	16.8	2.11
Butyl "	639.5	156.2 "			1.67
Amyl "	795.6	156.1 "	109.56 "	16.78	1.47
Hexyl "	951.9	156.3 "	126.34 "	16.75	1.37
Heptyl "	1108.4	156.5 "	143.09 "	16.67	1.27
Octyl "	1265.0	156.6 "	159.76 "	16.60	1.21
Nonyl "	1420.9	155.9 "	176.36 "	16.59	1.16
Decyl "	1576.9	156.0 "	192.95 "		1.12

¹ Δ constant.

² No oscillation is to be observed here.

³ At a given temperature the degree of association decreases as the homologous series is ascended.

⁴ $n = \left(\frac{T}{100 d_0} \right)^2$. See J. chim. phys. 1903, 1, 289.

XXVII. Atomic refractions ¹

For the three hydrogen lines, C (H α), F (H β), and G' (H γ), and the sodium D-line.

Atomic dispersion for H β — H α and H γ — H α (H = 1.008)

	Symbol	H α	D	H β	H γ	H β — H α	H γ — H α
CH ₂ -group.	CH ₂	4.598	4.618	4.668	4.710	0.071	0.113
Carbon	C	2.413	2.418	2.438	2.466	0.025	0.056
Hydrogen	H	1.092	1.100	1.115	1.122	0.023	0.029
Hydroxyl oxygen	O'	1.522	1.525	1.531	1.541	0.006	0.015
Ether oxygen.	O<	1.639	1.643	1.649	1.662	0.012	0.019
Carbonyl oxygen	O''	2.189	2.211	2.247	2.267	0.057	0.078
Chlorine.	Cl	5.933	5.967	6.043	6.101	0.107	0.168
Bromine.	Br	8.803	8.865	8.999	9.152	0.211	0.340
Iodine.	I	13.757	13.900	14.224	14.521	0.482	0.775
Ethylenic linkage	=	1.686	1.733	1.824	1.893	0.138	0.200
Acetylenic linkage	=	2.328	2.398	2.506	2.538	0.139	0.171
Nitrogen in primary amines	H ₂ N—C	2.309	2.322	2.368	2.397	0.059	0.086
" " secondary amines. . . .	HN—(C) ₂	2.478	2.502	2.561	2.605	0.086	0.119
" " tertiary amines. . . .	N—(C) ₃	2.808	2.840	2.940	3.000	0.133	0.186
" " imines (tertiary ²). . . .	C—N=C	3.740	3.776	3.877	3.962	0.139	0.220
" " nitriles	N \equiv C	3.102	3.118	3.155	3.173	0.052	0.060

¹ Calculated from the Lorentz-Lorenz equation $\frac{n^2-1}{n^2+2} \cdot \frac{M}{d}$ (Eisenlohr).

² The value for nitrogen in the imines and nitriles includes the increment for the double and triple nitrogen-carbon bond, respectively.

Important dates in the history of organic chemistry up to 1946¹

- 1760 Preparation of cacodyl from potassium acetate and arsenious acid by Cadet.
1769 Preparation of crystalline tartaric acid from argol by Scheele.
1772 Observation of the formation of methane in putrefaction processes by Priestley.
1773 Discovery of urea by Rouelle.
1775 Preparation of pure benzoic acid from benzoin (gum) (Scheele).
1776 Discovery of uric acid in urinary calculi and urine (Scheele, Bergmann).
1777 Separation of chemistry into "inorganic" and "organic" (Bergmann) — 1808, Berzelius used the term "organic chemistry".
1779 Preparation of glycerol from olive oil (Scheele).
1780 Discovery of lactic acid in sour milk (Scheele).
1785 Preparation of malic acid from apples (Scheele).
1786 Lavoisier observed that alcohol gave acetic acid on oxidation.
1789 Explanation of the general chemical course of alcoholic fermentation (Lavoisier).
1797 Fourcroy demonstrated that ether was produced from alcohol by removal of water.
1806 Morphine isolated as the first alkaloid from opium (Sertürner).
1811 Preparation of prussic acid in a state of purity by Gay-Lussac.
Kirchhoff prepared glucose by treating starch with sulphuric acid.
1815 Preparation of "free cyanogen" by Gay-Lussac.
Biot observed the optical activity exhibited by various organic substances, such as cane sugar, tartaric acid, etc., and in 1817, glucose.
1818 Isolation of chlorophyll from leaves (Pelletier and Caventou).
1819 Naphthalene discovered (Garden and Kidd).
1820 Preparation of caffeine from coffee by Runge (1821 also by Robiquet, Pelletier and Caventou).
1824 Synthesis of oxalic acid from cyanogen by Wöhler.
1825 Discovery of benzene in compressed oil-gas by Faraday.
1826 Tiedemann and Gmelin obtained hæmatin from blood.
1828 Etherin theory of Dumas.
Synthesis of urea from ammonium cyanate (Wöhler).
Preparation of nicotine from tobacco (Posselt and Reimann).
1830 Introduction of the idea of isomerism and polymerism (Berzelius).
Estimation of nitrogen by Dumas (improved 1833).
1831 Preparation of the first carotenoid pigment, carotene, from carrots (Wackenroder).
Preparation of chloroform and chloral from alcohol and chlorine and bleaching powder respectively (Liebig, Soubeiran, Guthrie).
1832 Anthracene isolated from tar (Dumas and Laurent).
Work of Liebig and Wöhler on the benzoyl compounds.
Laurent's investigations on naphthalene and its derivatives.
1833 Detection of "diastase" in germinating barley (Payen and Persoz).
1834 Aniline, quinoline, pyrrole, and phenol discovered in tar (Runge).
Theory of "contact action" in chemical reactions (Mitscherlich).
Dumas' substitution theory.
1835 Introduction of the idea of catalysis (Berzelius).
1836 Preparation of anthraquinone from anthracene and nitric acid by Laurent.
Preparation of phthalic acid from naphthalene by oxidation (Laurent).
1837 ff. Bunsen's work on cacodyl.
1838 Preparation of quinone from quinic acid (Woskresensky).
1839 Anti-vitalistic theory of fermentation (Liebig).

¹ Based in part on E. O. von Lippmann's "Zeittafeln zur Geschichte der organischen Chemie".

- 1841 Phenol prepared in a state of purity from coal-tar (Laurent).
- 1843 Introduction of the idea of "homologous series" by Gerhardt.
- 1844 Liebig's theory of fermentation.
- 1846 Elucidation of the constitution of ether by Laurent.
Preparation of nitrocellulose by Schönbein.
Preparation of nitroglycerine by Sobrero.
- 1847 Degradation of starch by diastase to maltose (Dubrunfaut).
- 1848 Resolution of racemic acid into the optically active tartaric acids by crystallization (Pasteur).
Discovery of the alkylamines by Wurtz.
- 1849 Preparation of the alkylanilines (A. W. Hofmann).
Kolbe's synthesis of hydrocarbons by electrolysis of solutions of salts of fatty acids.
- 1850 Theory of ether formation and preparation of mixed ethers by Williamson.
- 1851 Preparation of the tetraalkylammonium bases by A. W. Hofmann.
- 1852 Resolution of racemates by means of optically active bases (Pasteur).
Gerhardt's theory of types.
- 1853 ff. Synthesis of glycerides and fats by Berthelot.
- 1856 First synthesis of methane (Berthelot) from CS_2 and H_2S .
- 1857 Postulate of the tetravalency of carbon (Kekulé).
Glycogen isolated from liver (C. Bernard).
- 1858 Theory of linking of atoms in chains and conception of modern structural formulæ by Kekulé.
Discovery of aromatic diazo-compounds by P. Griess.
Resolution of racemates by the biochemical method (Pasteur).
- 1859 Pasteur's theory of the asymmetry of the organic molecule as the cause of its optical activity.
- 1860 Division of organic chemistry into aromatic and aliphatic or fatty compounds by Kekulé on the one hand, and by A. W. Hofmann on the other.
- 1862 ff. Preparation of crystalline hæmoglobin (Hoppe-Seyler).
- 1863 Preparation of acetylene from calcium carbide (Wöhler)
- 1865 Preparation of acetoacetic ester by Geuther.
Derivation of the formula of benzene (Kekulé).
- 1866 Derivation of the formula of naphthalene (Erlenmeyer).
- 1868 Synthetic preparation of alizarin from anthraquinonesulphonic acid (Caro, Graebe, Liebermann).
Preparation of hydroaromatic compounds by Graebe, Baeyer, Berthelot.
Preparation of lecithin from brain (Strecker).
- 1869—74 Proof of the equivalence of the six H-atoms in benzene by Ladenburg.
- 1870 Synthesis of indigo from isatin with phosphorus trichloride (Baeyer) and from nitroacetophenone (Engler and Emmerling).
Method of exhaustive methylation of A. W. Hofmann.
- 1873 Discovery of geometrical isomerism by Wislicenus.
- 1874 Theory of Le Bel and van 't Hoff on the tetrahedral arrangement of substituents about the carbon atom.
- 1875 Dimethyl ether hydrochloride with tetravalent oxygen (Friedel).
Explanation of the stereoisomerism of fumaric and maleic acid (van 't Hoff).
Discovery of phenylhydrazine by E. Fischer.
Preparation of coumarin by W. H. Perkin, sen. (Perkin's reaction).
- 1876 Rosaniline recognized as a derivative of triphenylmethane (E. and O. Fischer).
- 1877 Introduction of aluminium chloride as a catalyst (Friedel and Crafts).
Discovery of the laws of esterification by Menshutkin.
Detection of osmotic pressure in sugar solutions (Pfeffer).
- 1880 Synthesis of quinoline by Skraup.
- 1881 Degradation of aliphatic amides to amines by bromine and alkali (A. W. Hofmann).
Acetaldehyde prepared from acetylene (Kutscheroff).
Cannizzaro's reaction.
- 1882 Synthetic polypeptides (Curtius).
Investigation of the thiophen group by V. Meyer.

- 1883 Synthesis of antipyrine by Knorr.
Formula of indigo deduced by A. von Baeyer.
Preparation of the first tri-, tetra-, and pentamethylene derivatives by Perkin.
- 1884 Preparation of the first substantive cotton dye, Congo red, by Boettiger.
Invention of the Chardonnet artificial silk process.
Replacement of the diazo-group by halogen, cyanogen, and other radicals by Sandmeyer.
- 1884 ff. Beginning of the systematic investigation of the terpenes by Wallach.
- 1885 Baeyer's Strain Theory.
- 1886 First synthesis of an alkaloid by the artificial preparation of coniine (Ladenburg).
Discovery of aliphatic diazo-compounds by Curtius.
- 1887 Replacement of diazo-groups by other radicals (Sandmeyer).
Determination of molecular weights by osmotic pressure (van 't Hoff).
- 1888 Cis-trans isomerism (Baeyer).
Synthesis of uric acid from acetoacetic ester and isodialuric acid or urea (Behrend and Roosen).
- 1890 Stereoisomerism of the oximes (Hantzsch and Werner).
Preparation of azides (Curtius).
Synthesis of glucose by Emil Fischer.
First Heumann synthesis of indigo from phenylglycine-*o*-carboxylic acid.
Synthesis of fructose and mannose (Emil Fischer).
Invention of cuprammonium process for artificial silk (Despaissis).
- 1891 Preparation of viscose rayon (Cross, Bevan, and Beadle).
- 1892 Discovery of iodoso-, iodo-, and iodonium compounds by Victor Meyer.
- 1893 Elucidation of the formula of camphor by Bredt.
Coordination theory of A. Werner.
- 1896 W. Wislicenus and Knorr observed the reversibility of the conversion of keto and enol forms.
Claisen isolated the first keto and enol forms.
- 1897 Discovery of cell-free fermentation by Buchner.
Introduction of methods of catalytic reduction by Sabatier and Senderens.
- 1899 Discovery of basic properties of oxygen-containing organic compounds by Collie and Tickle.
Walden inversion.
- 1900 Discovery of triphenylmethyl (Gomberg).
- 1901 Discovery of alkylmagnesium salts by Grignard.
Discovery of anthraquinone vat dyes by R. Bohn.
Synthesis of polypeptides by E. Fischer.
Oxonium theory (Baeyer).
- 1902 Hardening of fats (Normann).
- 1903 Isolation of adrenaline as the first hormone (Takamine, Aldrich).
- 1904 Synthesis of nicotine by A. Pictet.
Discovery of ozonides (Harries).
First synthesis of a hormone (adrenaline) by Stolz.
- 1905 Discovery of the ketens (Staudinger).
- 1909 Total synthesis of camphor (Komppa).
- 1910 Preparation of salvarsan (= arsphenamine) by P. Ehrlich.
- 1911 Discovery of the diarylnitrogen compounds (Wieland).
- 1912 Formula of tannin put forward by E. Fischer.
Dehydrogenation theory of Wieland.
Introduction of organic microanalysis by Pregl.
- 1913 First anthocyanin prepared in state of purity (Willstätter).
Hydrogenation of coal and peat (Bergius).
- 1914 Addition of metals across multiple links by Schlenk.
- 1916 New method of formulating the homopolar link and organic compounds by G. N. Lewis.
- 1921 ff. Recognition of the isoprene rule as a wide-spread structural principle in nature (L. Ruzicka).
Recognition of rubber as a high-molecular hydrocarbon by Staudinger.

- 1922 Synthesis of methyl alcohol from CO and H₂ (Mittasch).
Resolution of biphenyl derivatives into optically active components (Kenner).
- 1923 Introduction of the isotope technique for the study of processes in the living cell with radioactive lead and later (1935) with radioactive phosphorus (v. Hevesy).
- 1925 Formulation of the sugars as δ -oxide cyclic hemiacetals by W. N. Haworth.
Elucidation of the constitution of the catechins and synthesis of *epicatechin* by Freudenberg.
Discovery of *cis*- and *trans*-decalin by W. Hüchel.
Resolution of sulphinic acids and sulfoxides (1928) into optically active forms (H. Phillips).
Discovery of the pterins by Wieland.
- 1926 Preparation of multi-membered carbon rings by Ruzicka.
Elucidation of the constitution of, and synthesis of thyroxine, by Harington.
Isolation of vitamin B₁ in the crystalline form by Jansen and Donath.
Vitamin D-preparations made by irradiation of ergosterol (Windaus and Pohl, Rosenheim, Hess).
- 1928 Isolation of vitamin C by Szent-Györgyi.
Diene synthesis of Diels and Alder.
Discovery of penicillin by Fleming.
- 1929 Resolution of racemates by means of circularly polarized light (Werner Kuhn).
Synthesis of hæmin by Hans Fischer.
- 1929 ff. Isolation of the follicular hormones (Butenandt, Doisy, Girard, Marrian)
- 1930 Formulæ of carotene and lycopene put forward (P. Karrer).
- 1931 Synthesis of anthocyanins by R. Robinson.
Elucidation of the constitution of vitamin A (P. Karrer).
Preparation of vitamin D in a state of purity (Bourdillon and co-workers, Windaus).
- 1932 Discovery of the flavin enzyme (yellow oxidation ferment) by Warburg.
- 1932 ff. Isolation of the first testicular hormone (Butenandt, Laqueur etc.).
New formula for the sterols put forward (Rosenheim-Wieland).
- 1932-33 Preparation of the first organic compound with *heavy hydrogen* by Urey and other investigators.
Preparation of Nylon (Carothers, E. I. duPont de Nemours & Co.).
- 1933 New theory of alcoholic fermentation and break-down of sugars in muscle (Embden, Meyerhof).
Isolation of vitamin B₂ (R. Kuhn).
Synthesis of vitamin C (Reichstein, Haworth and Hirst).
Preparation of multi-membered rings according to the Ruggli dilution principle by K. Ziegler.
Isolation of the carcinogenic hydrocarbon 3:4-benzpyrene from coal-tar by Cook.
- 1934 Isolation of auxins (Kögl).
Isolation and synthesis of the hormone from the corpus luteum (Slotta, Hartmann and Wettstein, Butenandt, Fernholz).
Partial synthesis of androsterone (Ruzicka).
Discovery of the phthalocyanines (Linstead).
- 1935 Recognition of virus-matter as chemical compounds by Stanley.
Isolation (Laqueur) and synthesis (Butenandt, Ruzicka, Wettstein) of testosterone.
Discovery of the antibiotic activity of prontosil by G. Domagk, and of *p*-amino-benzenesulphonamide by Tréfouel, Tréfouel, Nitti, and Bovet.
- 1935-36 Isolation and elucidation of the constitution of the codehydrases I and II (H. von Euler, O. Warburg).
- 1936 Elucidation of the constitution and synthesis of vitamin B₁ by R. R. Williams, Windaus, Grewe and others.
The first preparation of pure biotin by Kögl.
- 1936-38 Isolation, elucidation of the constitution, and synthesis of vitamin E (α - and β -tocopherol) (H. M. Evans, Fernholz, P. Karrer).
- 1937 ff. Isolation and elucidation of the constitution of corticosterone by Reichstein and also by Kendall.

- 1938-39 Isolation, elucidation of the constitution, and synthesis of vitamin B₆ (pyridoxine) by György, R. Kuhn and co-workers, Itiba and Miti, as well as chemists of the Merck Company (Rahway).
- 1938-40 Elucidation of the constitution of pantothenic acid by R. J. Williams and co-workers, syntheses by Folkers *et al.*, R. Kuhn and co-workers, etc.
- 1939 Isolation, elucidation of the constitution, and synthesis of vitamin K (P. Karrer, E. A. Doisy, L. F. Fieser).
Enzymatic synthesis of glycogen from glucose-L-phosphate (G. T. Cori).
- 1939-44 Closer investigation and elucidation of the constitution of penicillin by co-operation of numerous English and American research-groups (in particular Florey, Chain, W. Baker, H. T. Clarke, J. R. Johnson, R. Robinson, etc.).
- 1940 In vitro synthesis of starch from glucose-L-phosphate and enzyme (C. S. Hanes).
- 1941 Discovery of a method of chlorination of olefins in the allyl position (Groll and Hearne).
Discovery of folic acid (pteroylglutamic acid) by Mitchell, Snell, and R. J. Williams.
- 1942 Introduction of the method of bromination by means of bromosuccinimide by Ziegler. Elucidation of the constitution of biotin by du Vigneaud.
- 1944 First syntheses of pterins (R. Purrmann).
Synthesis of quinine (R. B. Woodward).
Enzymatic synthesis of cane sugar from glucose-l-phosphate and fructose (W. Z. Hassid).
First synthesis of biotin (S. A. Harris *et al.*).
Discovery of streptomycin by A. Schatz, E. Bugie, and S. A. Waksman.
- 1945 Synthesis of *cyclooctatetraene* from acetylene by Reppe.
- 1946 Elucidation of the constitution and synthesis of folic acid (pteroylglutamic acid) by large groups of chemists of the Lederle Lab. Inc. and the Calco. Chem. Division, American Cyanamid Co. (U.S.A.).

INDEX

Stereoisomers and, in most cases, position isomers are indexed collectively except when their common names differ.

References marked with an asterisk indicate the pages on which physical constants are given.

Abbreviations

a = ana, 813
d-form, 99
d (+) (—) form, 105
d, *l*-form, 102
D-series, 105
 Δ , 178, 667
des, 743
F (increment), 52, 246
f (increment), 66
gem (geminal), 156, 663
i-form, 102
l-form, 99
l (+) (—) form, 105
L-series, 105
m (meta), 382
ms (meso), 410, 468
 μ (meso), 468
n (normal) form, 24
o (ortho), 382
p (para), 382
 ω , 331

Endings

-al, 158
 -ane, 23
 -ene, 49
 -o, 25
 -ol, 81
 -one, 172
 -yl, 23
 -ylene, 49
 -yne, 66

Abietic acid, 707
 Abrine, 787
 Acenaphthene, 384, **409***, 531
 Acenaphthenequinone, 409, 575
 Acenaphthylene, 409*
 Acetaldehyde, 70, 87, 91, 93, 160*, **168**, 846, 864
 Acetal phosphatides, 219
 Acetals, 93, 158, 159, **162**
 Acetamide, 224*

Acetanilide, 463, 464, **469***
 Acetate rayon, **364**, 486
 Acethydroxamic acid, 226*
 Acetic acid, 1, 12, 16, 72, 87, 194*, **200***, 838, 914*
 —, salts, 201, 486
 Acetic anhydride, 72, 222*
 Acetic fermentation, 200
 Acetin, 621
 Acetoacetic acid, 177, 197, 263, **267**
 —, ester, 174, **267***, 551, 646, 809
 —, allyl derivatives, 436
 —, C-acyl derivatives, 259, 269
 —, C-alkyl derivatives, 269
 Acetobromoglucose, **328**, 351
 Acetobromomaltose, 358
 Acetochloroglucose, 301
 Acetoin, 257*
 Acetol, **256***, 258
 Acetone, 57, 62, 72, 87, 174*, **176**, 263
 Acetone caoutchouc, 178
 Acetonecarboxylic semi-ester, 859
 Acetone-chloroform, 178
 Acetone dicarboxylic acid, **320**, 550, 906, 907
 —, ester, 855, 863
 Acetone-quinide, 689
 Acetonitrile, 188*
 Acetonyl-acetone, **261***, 757
 Acetophenone, 155, **514***, 555, 815
 Acetylacetonates, 260
 Acetylacetone, **259***, 271
 β -Acetylacrylic ester, 713
 γ -Acetylbutyric acid, 437
 Acetylcholine, 249
 Acetyl chloride, 221*
 Acetyl cyanide, 266
 Acetylcyclobutane, 650*
 Acetyldibenzoylmethane, 516*

Acetylene, 3, 26, 27, 62, 66, **68**, 69*, 384, 649, 747, 796, 800
 Acetylene-*d*₂, 912
 Acetylenes, **66**
 —, metallic derivatives, 67, 71
 —, nomenclature, 66
 Acetylene tetrachloride, 70, 252*, 909*, 910*
 Acetylenic carboxylic acids, 210
 Acetylenic linkage, 66
 Acetyl-*isoeugenol*, 508, 540
 N-Acetylglucosamine, 349
 α and β -Acetylglucose, 301
 Acetylides, 68, 71, 705
 Acetylleucine ester, 790
 Acetylmezcaline, 852
 Acetyltoluidides, 457*, 535
 Acids, see Amino, Carboxylic, Sulphonic, Unsaturated etc.
 γ -Acid, 468
 Acid alizarin black SE, 492
 Acid amides, 65, 83, 130, 195, **223**, 511, 523, 790, 802
 Acid anhydrides, 196, **221**, 522
 Acid black 4 B, 489
 Acid function, 190ff
 "Acid" hydrolysis, **270**, 317
 Acid (or acyl) radical, 190
 Aci-form, 139, 422, 448, 475, 913
 Aconines, 903
 Aconitic acid, 284, **319**, 320, 691, 838
 Aconitine, 903
 Acridine, 384, 615, **630***
 Acridine dyes, 630
 Acridine hydrides, 631
 Acridine orange NO, 631
 Acridine yellow, 632
 Acridinic acid, 631
 Acridinium yellow, 632
 Acrolein, 109, **169***, 205, 311, 811

- α -Acrose, 167, 343
 Acrylic acid, 205, **207***, 263
 —, ester, 79, 818
 —, series, 205
 Acrylonitrile, 189
 Activation, benzene substituents, 415, 420, 497
 —, methylene group, 140, **164**, 196, 259, 267, 398, 405, 515, 525, 653, 809, 913
 Acylation, 222, 431
 Acyloins, 267
 N-Acyl-pyrroles, 769
 Acyl radical, 190
 Adaline, 232
 Adamkiewicz reaction, 306
 Adenase, 828
 Adenine, 731, 826, **828***, 830
 Adenosine, 830, 832
 Adenosine phosphates, 92, 830
 Adenylic acid, 92, 830, 832, 833
 Adenyl phosphate, 732
 Adermine, 732
 Adipic acid, 198, 274*, 275, **280**, 640, 654, 665, 737
 Adipic acid ester, 639
 Adipic acid, methyl substituted, 667, 710
 Adonitol, **313***, 335
 ADP, 831
 Adrenal cortex hormones, 724
 Adrenaline, 101, **462***, 724, 837
 Aenin, 564
 Aesculetin, 552*
 Aesculin, 552
 Aetiobiliaric acid, 727
 Aetiocholanic acids, 725
 Aetioporphyrin, 773, 778
 Aglycones, 725
 Agmatine, 233
 Agurin, 828
 Alanine, 266, 286, 289*, 300, 304, 308, 737, 787
 Alanine ester, 304
 Alaninol, 901
 Albumins, 288, 305, **307**
 Albumoses, 307
 Alcohol, see Ethyl alcohol
 Alcohols, aliphatic, dihydric, see Glycols
 —, —, monohydric, 28, 50, 54, 73, **80**, 117, 292, 941
 —, —, polyhydric, 308
 —, —, polyhydric, preparation 81
 —, —, polyhydric, properties, 84
 —, —, polyhydric, primary, 82, 158, 160, 195, 391
 —, —, polyhydric, secondary, 83, 173, 174, 391
 —, —, polyhydric, tertiary, 50, 83, 174
 Alcohols, aromatic, 450
 —, nomenclature, 81
 Alcoholates, 86
 Alcoholic beverages, 95
 Alcoholic fermentation, 89, 344
 Alcoholoxidase, 200
 Alcoholysis, 212
 Aldehydes, aliphatic, 55, 82, 86, 117, **158**, 244, 263, 653, 809, 812, 816
 —, aromatic, 450, **504**, 653
 —, ketonic, 791, 796
 —, nomenclature of, 158
 —, unsaturated, 164, **169**, 205, 507, 796
 Aldehyde ammonias, 163
 Aldehyde bisulphite compounds, **160**, 505
 Aldehydeketones, 257, 459
 Aldehydic carboxylic acids, 265
 5-Aldehydo-pyromucic acid, 742
 Aldimines, 104, 129, 292, 506
 Aldol, 61
 —, condensation, **164**, 167, 170, 342, 344, 441
 Aldolase, 91
 Aldonic acids, 325, 331
 Aldose oximes, 325, 331
 Aldoses, 255, 264, **321**, 329, 331, 332, 344
 Aldoximes, **162**, 188, **514**
 Alecoronic acid, 542
 Algol red B, 604
 Algol red 5 G, 604
 Algol yellow G, 604
 Alicyclic compounds, 637
 —, higher ring systems, 746
 —, ring fissure, 640, 694, 698
 —, stereochemistry, 408, 647, 651, 657, 663
 —, synthesis, 638
 Alizarin, 1, **592**, 595*
 Alizarin black S, 589
 Alizarin blue, 596
 Alazarin bordeaux, 597
 Alizarin brown, 598
 Alizarin cyanin R, 597
 Alizarin cyanin green G, 600
 Alizarin-indigo 3 R, 576
 Alizarin orange, 596
 Alizarin pure blue B, 600
 Alizarin-saphirole A, 600
 Alizarin-saphirole B, 601
 Alizarin yellows, A and C, 519
 —, GGW and R, 491
 Alkali blue, 614
 Alkali metals, organic compounds, 155, 503
 Alkaloids, **837**
 —, classification, 837
 —, isolation, 838
 —, occurrence, 837
 —, biological formation, 905
 Alkanes, 23
 Alkannin, 589*
 Alkathene, see Polythene
 Alkenes, 49
 Alkoxoacids, 86
 Alkoxymethylene compounds, 220
 Alkylation, 112, 115, 128, 390, 425, 430, 455
 Alkylenes, 49
 Alkylene oxides, 244, 248
 Alkyl oxides, see Ethers
 Alkylpyrroles, 769, 771
 Alkyl radicals, 23, 29
 Alkynes, 66
 Allantoin, 824*, 919
 Allantoinase, 824
 Allelotropy, 109
 Allene, 59*
 Allenes, stereochemistry, 690
 Allicin, 120
 Alliin, 123
 Allophanic acid, 232
 Allose, 337–341, 339*
 Alloxan, 279, 315, **317**, 730, 824
 Alloxantin, 825
 Allulose, 339
 Allyl alcohol, 78, 87, **109***, 169, 255
 Allylbenzene, 155
 Allyl bromide, 79*
 Allyl chloride, 77, **79***, 309
 Allyl cinnamate, 79
 Allylene, 77
 Allylene halides, 78
 Allyl iodide, 79*
 Allyl rearrangement, 109, 434, 436, 659
 Allyl salicylate, 79
 Allyl isothiocyanate, 240*
 Aloe-emodin, 599*
 Altrose, 337–341, 339*
 Aluminium acetate, 201, 595
 Aluminium acetylacetonate, 260*

- Aluminium alcoholate, 86
 Aluminium, organic compounds of, 151
 —, tri-ethyl, 151*
 —, tri-methyl, 151*
 Amarine, 505
 Ambrette musk, 421
 Ambrettolide, 265
 Amethyst violet, 619
 Amidines, **225**, 818
 Amidobromides, 242
 Amines, aliphatic, 87, **124**, 740
 —, —, preparation, 128
 —, —, properties, 131
 —, —, primary, 82, 84, 153, 176, 189
 —, —, secondary, 153, 189
 —, —, tertiary, 133, 236
 Amino acids with heavy nitrogen, 918
 Amines, aromatic, 427, **451**, 481, 811, 812
 —, —, N-acylated, 469
 —, —, primary, 454, 577
 —, —, tertiary, 482, 505
 Amines, cyclic, 383
 —, proteinogenic, 291, 837, 840
 Amine oxides, 126
 Aminoacetophenones, 786, 816
 ω -Amino-aceto-veratrone, 877
 Amino-acids, aliphatic, 126, 254, **285**, 641, 810, 821
 —, —, N acyl derivatives, 286, 290
 —, —, esters, 248, 290, 790, 791, 822
 —, —, salts and complexes, 290
 —, —, stereochemistry, 300
 —, aromatic, 533
 —, relation to alkaloids, 905
 Amino-alcohols, 244, **247**, 290, 644
 Amino-aldehydes, 248
 Aminoanthraquinones, 592, **599**, 601
 4-Amino-antipyrine, 799
 Aminoazobenzene, 460, 482, **487**
 Aminoazocompounds, 482, 801
 Aminobarbituric acid, 279
 See also Uramil
 Aminobenzaldehyde, 812
 2-(*p*-Aminobenzenesulphonamide)-pyridine, 808
 2-(*p*-Aminobenzene-sulphonamido)-thiazole, 792
o-Aminobenzenesulphonic acid, 466
 Aminobenzoic acids, 534*, 733
p-Aminobenzoylglutamic acid, 739
 Aminobenzoyl-pyruvic acid, 787
o-Aminobenzylamine, 474
 Aminobutyric acids, 287, 289*, 810
 Aminocaproic acids, 286, 287, 682
 δ -Aminocaprylic acid, 846
 3-Aminocarbazole, 629
 1-Amino-2-carbethoxyamino-4:5-dimethylbenzene, 730
 α -Amino- β -chloropropionic acid, 302
 β -Aminocrotonic ester, 813
 Aminodihydroxypurine, 829
 Aminodimethylbenzenes, 457*
 Aminoethyl alcohol, 248*
 See also Colamine
 3-[β -Aminoethyl]indole, 899
 Amino-G-acid, **467**, 489
 Aminoguanidine, 803
 Aminohydroxypyrimidines, 819, 825, 829
 Aminoketones, 248, 769, 790, 791, 821
 Amino methanols, 163
 Aminonaphthalenes, see Naphthylamines
 Aminonaphthols, 483, 491
 1-Amino-8-naphthol-2:4-disulphonic acid, 494
 1-Amino-8-naphthol-3:6-disulphonic acid, 468
 2-Amino-8-naphthol-6-sulphonic acid, 468
 α -Aminonitriles, 285
o-Aminophenol, **468***, 473, 491
m-Aminophenol, 430, **468***, 621, 634, 904
p-Aminophenol, 423, **468***, 473, 580, 583, 584, 626
o-Aminophenylacetaldehyde, 784
p-Aminophenylarsonic acid, **501**, 502
o-Aminophenyl-glyoxylic acid, 568
 Amino-polypeptidase, 307
 β -Aminopropionic acid, 299, 810
 Amino-purines, 828
 Aminopyrazole, 797
 Aminopyridines, 807
 γ -Aminoquinoline, 473
 Amino-R-acid, **467**, 489
 5-Aminoresorcinol, 430
o-Amino-*cis*-stilbene, 411
o-Aminostilbene-carboxylic acid, 411
 Amino-sugars, 348
 Aminotetrazoles, 803
 α -Aminothiophen, 765
 Aminotriazole, 836
 δ -Aminovaleric acid, 810
 Ammelide, 238
 Ammeline, 238
 Ammoniacal liquor, 383
 Ammonia type, 20
 Ammonium compounds, 126
 Ammonium salts "internal", 134
 Amygdalin, **184**, 504, 548
*iso*Amyl acetate, 97, **211***
 Amyl alcohols, 93, 97*
 Amyl alcohol, *n*, 85*, **97**
 —, optically active, **97***, 100
n-Amyl amine, 131*
*iso*Amyl amine, 291
 Amylases, 358
n-Amyl bromide, 74*
*iso*Amyl butyrate, 97, 211*
 Amyl chloride, 74*
 Amyl cyanide, 188*
 5-Amyl-1:3-cyclohexanedione, 553
*iso*Amyl-dihydrocupreine, 851
 Amylene, 52*, 97
 Amylene-hydrate, 97*
*iso*Amyl ether, 115
 Amyl iodide, 74*
 Amyl mercaptan, 119*
 Amyl nitrite, **112**, 472, 556
 Amylopectin, 357
 Amylose, 357
 Amyloses, crist., 359
n-Amyl-*n*-propyl ketone, 864
*iso*Amyl isovalerate, 97, **211***
 Ana, 813
 Anabasine, 843, 853
 Anaesthesin, 535*
 Androstane, 722
 Androstanedione, 723
 Androstenedione, 723
 Androsterones, 722, 723
 Anethole, 432, **434***, 507, 537
 Aneurin, 729
 Angelic acid, 208*
 Angelicin, 763
 Anhalamine, 875
 Anhalinine, 875
 Anhalonidine, 875
 Anilides, 454, **469**, 514

- Aniline, 373, 430, **454***, 570, 579, 610, 612
 Aniline black, 585
 Aniline blue, 614
 Aniline sulphonic acids, 465, 471
 Aniline yellow, 487
 An linohydroquinone, 577
 An linoquinone, 577
 Anisaldehyde, 507*
 Anisic acid, 431, 513, **537***
 Anisidines, 435, **469**
 Anisole, 432*
 Annulation, 412
 Anol, 434*
 Anserine, 299
 Antheraxanthin, 711
 Anthocyanidins, 563
 Anthocyanins, 562
 Anthracene, **409***, 591
 Anthracene blue WR, 597
 Anthracene brown, 598
 Anthracene oil, 383
 Anthragallol, 597
 Anthrahydroquinone, 591*
 Anthranilic acid, 373, 375, **534***, 571, 574
 Anthranol, **443***, 575
 Anthrapurpurin, 597
 Anthraquinone, 409, 443, **591***
 Anthraquinone-acridone dyes, 605
 Anthraquinonedisulphonic acids, 592, 593
 Anthraquinone imine dyes, 603
 Anthraquinonesulphonic acids **592**, 593, 595, 838
 Anthraquinone violet, 600
 Anthrarufin, 596
 Anthrone, **443***, 592
 Anthropo-deoxycholic acid, 716, 717
 Antifebrine, 469
 "Anti-knock", 150
 Antimony compounds, aliphatic, 145
 Antimony, aromatic, 503
 Antipodes, optical, 99, **101**, 107
 Antipyrine, **270**, 797, 798, 799*
 Apigenidin, 563, 564
 Apigenin, 556*
 Apiin, 345, 556
 Apioles, 441*
 Apionic acid, 345
 Apiose, 322, **345**
 Apocamphoric acid, **657**, 703
 Apocyn.n, 517
 Apomorphine, 892
 Aponal, 230
 Aponarceine, 883
 Apophyllenic acid, 879
 Aposafnanines, 617, **618**
 Araban, 357
 Arabinose, **334**, 337, 344, **345*** 355, 357, 365
 Arabitols, **313***, 335
 Arabonic acid, 344
 Arachidic acid, 193*, 203
 Arachidonic acid, 215
 Arbutin, 438
 Areca alkaloids, 849
 Arecaidine, 850*
 Arecoline, 850*, 863
 Arginine, 251, 287, 288, 289*, 308, 918
 Arginine-phosphoric acid, 295
 Aristol, 433
 Arndt and Eistert reaction, 193, 916
 "Aromatic" character, 379, 758, 765, 769
 Aromatic compounds, 373
 Arsacetin, 501
 Arsenic compounds, aliphatic, **143**
 —, aromatic, 500
 Arsenic, estimation of, 8
 Arsenic oxides, 501
 Arseno-compounds, 501
 Arsines, **143**, 144, 500, 501
 Arsonic acids, 143, 144, 477
 Arsonium compounds, 143
 Arsphenamine, 502
 Artificial materials, 938
 Asarones, 439*
 Ascorbic acid, 733
 Asparagine, 106, 288, 289*, 302
 Aspartic acid, 287, 288, 289*, 300, 304, 918
 —, ester, 304
 Aspergillic acid, 822
 Asphalt, 41, 42
 Aspirin, 536*
 Association, 12, 85, **127**, 194, 224, 795
 Astacin, 712
 Astaxanthin, 712
 Asymmetrical (*as*), 382
 Asymmetric carbon atom, 99
 Asymmetricmolecule, 101, 664
 Asymmetric syntheses, 104, 548
 A.T. 10, 735
 Atebrin, 633*
 Atomic distances, 380
 Atomic refraction, 941
 Atophan, 815
 Atoquinol, 815
 Atoxyl, 501
 ATP, 831
 Atrolactyl-tropeine, 857
 Atromentic acid, 580
 Atromentin, 580
 Atropic acid, 525, 527, 549
 Atropines, 768, 845, 853, 857, 858, 907
 Aurantia, 465
 Aurichlorides, alkyl, 155
 Aurin, 609
 Auroxanthin, 711
 Autoxidation, 504
 Auxins, 658, 659
 Auxochromes, 483, **485**
 Aviation spirit, 36
 Avidin, 738
 Axerophthol, 728
 Azafrin, 712
 Azelaic acid, 198, 204, 274*, 275, **281**, 746, 751
 Azelaone, see Cyclooctanone
 Azides, acid, 130, 195, **226**, 523, 800
 —, aryl, 477
 Azido-propiono-dimethyl amide, 105
 Aziminobenzene, 801*
 Aziminotoluene, 802*
 Azinepurine, 833
 Azobenzene, 481, 484, 497
 Azocarmine G, 618
 Azo-compounds, 8, 451, **481**, 496, 497, 804
 Azo-dyes, 481, **487**, 770, 799
 Azoimides, 801
 Azoimidobenzene, 458
 Azoles, 789
 Azophenine, 577*
o,o'-Azoxyanisole, 497
 Azoxybenzene, 423, **496***
 Azoxy-compounds, 451, **496**, *o,o'*-Azoxytoluene, 497
 Azulenes, 744
 Azulmic acid, 272
 Baeyer's strain theory, see Strain theory
 Bakelite, 168, 432
 Balata, 741
 Barbituric acid, **279**, 913
 —, C-dialkyl derivatives, 279
 Barium platinocyanide, 187
 Bathochromic group, 485
 Batyl alcohol, 310
 "Bayer 205", 470

- Beckmann rearrangement, 512, 641
- Behenic acid, 33, 203
- Benzal-acetophenone, 516*
- Benzal chloride, 399, **417***, 504
- Benzaldehyde, 160, 420, 450, **504***, 525, 610, 917
- Benzaldehydecyanhydrin, 548
- Benzaldoximes, 514*
- 9-Benzal-fluorene, 398
- Benzal-indene, 405
- Benzalindoxyl, 568
- Benzamide, 523*
- Benzanilide, 469
- Benzanthrone, 602
- Benzaurin, 609
- Benzazide, 523
- Benzedrine, 463
- Benzene, 3, 69, **383**, 384*, 455, 642, 665, 914*
- , configuration, 380
- , constitution, 374, 381
- , formulae, 377
- Benzene-azomalononitrile, 826
- Benzene disulphonic acids, **424**, 429, 437, 439
- Benzene hexabromide, 386
- Benzene hexachlorides, 386
- Benzene homologues, 390, 418, 523, 642
- Benzene ozonide, 387, 389
- Benzene pentacarboxylic acid, 531*
- Benzene sulphinic acid, 426
- Benzene sulphonamides, 128
- Benzene sulphonic acid, 385, **424**, 521, 524
- , methyl ester, 425
- Benzenesulphonyl chloride, 128, **425**, 513
- Benzene trisulphonic acid, **424**, 440
- Benzidine, 492, **498**, 630
- Benzidine rearrangement, 498, 785
- Benzil, 515*
- Benzildioximes, 515*
- Benzilic acid, 515, 759
- Benzilic acid rearrangement, **515**, 656
- Benzil monoximes, 513*
- Benzimidazoles, 459
- Benzimido-ether, 523*
- Benzine, see Petroleum
- Benzocaine, 535*
- Benzoflavine, 633
- Benzohydrazide, 523*
- Benzohydroxamic acid, 523*
- Benzohydroximic acids, 524
- Benzoic acid, 1, 18, 373, 374, 450, 505, **521***, 555, 597, 859, 914*
- , methoxyanilide, 514
- Benzoic anhydride, 522*
- Benzoin, 459, 505, **515***
- Benzoin condensation, 343, **505**, 759
- Benzonitrile, 462, 503, 513, 521, **524***
- Benzophenone, 398, **514***
- Benzopurpurine 4B, 493
- o*-Benzoquinone, 576, **580**
- p*-Benzoquinone, 60, 282, 439, 461, **576**, 579*, 606, 654
- p*-Benzoquinone oximes, 577, **582***
- Benzotriazine, 834
- Benzotriazole, 801*
- Benzotrichloride, 417*, 609, 610, 634
- Benzoxazoles 468
- Benzoyl-acetic acid, 853
- Benzoylacetone or Benzoyl-acetylmethane, 515*
- Benzoylamino compounds, 522
- Benzoyl aspartic acid, 302
- o*-Benzoyl-benzoic acid, 409, 591
- o*-Benzoyl-bromobenzoic acid, 409
- Benzoyl chloride, 431, **522***
- Benzoyllecgonine, 862*
- , ethyl ester, 860
- 9-Benzoyl-fluorene, 398
- Benzoyl-histidine, 302
- Benzoylphenylurea, 515
- N*-Benzoyl-piperidine, 241, 286, 810
- N*-Benzoyl-pyrrolidine, 242
- N*-Benzoyl-serine, 790
- Benzoyltropeine, 857
- Benzoyltropines, 862
- N*-Benzoyl-tyrosine, 302
- Benzpyrenes, **412***
- Benzyl alcohol, **450***, 504, 505, 521
- Benzylamine, 462*, 524
- Benzylaniline, 631
- o*-Benzylbenzoic acid, 443
- p*-Benzyl-biphenyl, 391
- Benzyl bromide, 418*
- Benzyl chloride, 391, **417***, 450, 462
- Benzyl cyamide, 462
- Benzyl esters, 451
- Benzylideneacetone, 526
- Benzyl iodide, 418*
- 2-Benzyl-4-methoxymethylene-oxazolone, 793
- Benzyl-phenyl-allyl-methylammonium salts, 134
- Benzyl-pyrrole, 771
- Berberal, 884
- Berberilic acid, 884
- Berberine, 884, 887, 897
- Berberonic acid, 811*, 885, 898
- Bergapten, 763
- Bergaptol, 763*
- Bergenin, 552
- Berilic acid, 884
- Betaines, 76, 126, 134, **295***, 787, 796, 798, 837, 842, 849
- Betonicine, 842*, 905
- Bibenzyl, 399*
- Bicyclo-octatriene, 747
- Biebrich scarlet, 489
- Bifuchsonyl, 581
- Bile acids, 713, **716**
- Bilirubic acids, 776
- Bilirubin, 772, 776, 782
- Bindschedler's green, **584**, 624
- Bios I, 676
- Bioses, 321
- Biotins, 733, 737
- Biphenyl, 155, 384, **395***, 411, 479
- Biphenyl derivatives, stereochemistry of, 395
- Biphenyl dicarboxylic acid, 531
- Biphenylene ethylene, 404, 654
- Biphenyleneglycolic acid, 590
- Biphenylene oxide, 764*
- Biradicals, 401
- Bisabolene, 705
- Bisabolol, 706
- Bismarck brown, 460, **487**
- Bismuth trialkyls, 145
- Bismuth triethyl, 145*
- Bismuth trimethyl, 145*
- Biuret, 232
- Biuret reaction, 232, 297, 306
- Bixin, 712, 713
- Blasting gelatine, 310
- Bohn-Schmidt reaction, 596
- Boletol, 598
- Bordeaux B, 488
- Boric acid, complexes, 114, 536
- , esters, **114**, 151, 391
- Borneo camphor, 700
- Borneols, 105, **700***, 702
- Bornesitol, 676
- Bornyl chloride, 698, 700, 702

- Bornyl esters, 702
 Bornyl iodide, 700
 Boron, organic compounds of, 151, 536
 —, —, optically active, 536
 Boron oxonium fluorides, 118
 Boron trialkyls, 151
 Boron triisobutyl, 151*
 Boron triethyl, 151*
 Boron trimethyl, 151*
 Boron triphenyl, 151
 Boron tripropyl, 151*
 Borosalicylic acid, 536
 Boroxides, 151
 Bouveault and Blanc reaction, 83, 196
 Brasan, 764*
 Brasilin, 764
 Brassidic acid, **209***, 284
 Brassylic acid, 209
 Brazilein, 561
 Brazilin, 561
 Brilliant acridine orange, 633
 Brilliant alizarin blue, 626
 Brilliant croceine 9 B, 489
 Brilliant green, 611
 Brilliant safranin, 619
 Brilliant yellow, 494
 Bromides, acyl, 195, **220**
 Brominal, 232
 α -Bromoaceto phenone, 791
p-Bromoaniline, 466
 Bromo-anthraquinone, 410
 Bromoazoxybenzenes, 496*
 Bromobenzene, 414*, 521
p-Bromobenzenediazo cyanide 476*
p-Bromobenzene nitrile, 476
p-Bromobenzenesulphonic acid, 426
 Bromobenzoic acids, 375, 533
 Bromocamphorsulphonic acid, 104, 701
 α -Bromodimethyl-acetyl bromide, 180
 Bromoform, **183***
 5-Bromo-2-furyl acrylic ester, 388
 4-Bromogentisic acid, decamethylene ether, 398*
p-Bromophenyl nitromethane, 422
 Bromopropionaldehyde, 840
 Bromopropionic acid, 300, 304
 —, ester, 105
 Bromopyridines, 808
 Bromoquinotoxine, 849
 Bromostyrene, 526
 Bromosuccinic acid, 282, 300, 304
 Bromosuccinimide, 53, 78
 Bromothymol-blue, 610
 Brucine, 104, 904
 Buchu-camphor, 687*
 Bufotalin, 726
 Bufotenidin, 787
 Bufotenine, 787
 Bufotoxin, 726
 Bulbocapnine, 888
 Buna, 115, 741
 Buna N, 189, 741
 Buna S, 741
 Butadiene, **61***, 69, 402, 483, 649, 741
 Butanes, 23, 30*, **35**, 649
*iso*Butanal- α,β - d_2 -diethyl-acetal, 912
*iso*Butane, **35**, 36
 2:3-Butanediol, 247
 Butein, 520
 Butene-(1) or butylene-(1), 42, 49, 52*, **57**
 Butene-(2), 49, 57
*iso*Butene or *iso*Butylene, 36, 42, 46, 56, 58, 79, 741
 Butin, 520
 Butyl alcohol, 85*, **96**
 —, *iso*-, 46, 53, 88, 93, 96*
 —, *sec*-, 57, **96***, 106
 —, *tert*-, 58, **96***
 Butylamine, 131*
*iso*Butyl boric acid, 151*
 Butyl bromide, 74*
 Butyl chloride, 74*
 Butyl cyanide, 188*
 Butylidene-phthalide, 530
 Butyl iodide, 74*, 77*
*iso*Butyl iodide, 35, **77***
 Butyl mercaptan, 119*
 Butyl-phthalide, 530
 α -Butylpyrrolidine, 250
 Butyl *isothiocyanate*, 241*
 Butyltoluene, 394*
 Butyne-(1), 67
 Butyraldehyde, 160*
 Butyric acid, 63*, **202**, 194*, 197
*iso*Butyric acid, 192, **202***
 Butyric anhydride, 222*
 Butyric fermentation, 202
 γ -Butyrolactone, 280
 Butyrone, 174*
 Butyryl chloride, 221*
*iso*Butyrylformic acid, 901
 Cachou de Laval, 626
 Cacodyl, 19, **144**
 Cacodyl compounds, 143
 Cacodyl hydride, 144
 Cacodyl oxide, 144
 Cacodylic acid, 145
 Cadalene, 706
 Cadaverine, 251*, 291
 Cadinene, 706
 Cadmium di-ethyl, 154*
 —, di-methyl, 154*
 —, di-propyl, 154*
 Caffeic acid, 543
 Caffeine, 543, **828**
 Calciferol, 735*
 Calcium butyrates, 202
 Calcium carbide, 69, 71
 Calcium cyanamide, 236
 Caledon Jade green B, 603
 Callistephin, 563
 Camphane, 693, 698, 699, **700**
 Camphane-2:3- d_2 , 912
 Camphanic acid, 699
 Camphene, 702
 Campholide, 701
 Camphor, 198, **699***, 702
 Camphors, 637, 693, 699
 Camphor π -carboxylic acid, 193
 Camphorene, 707
 Camphoric acids, 657*, 699, **700***
 Camphoric anhydrides, 700*
 Camphoronic acid, 699
 Camphor-quinone, 701
 Camphor sulphonic acid, 104, 701
 Canadine, 886, 887
 Cane sugar, see Sucrose
 Cannabidiol, 552
 Cannabinol, 552, 553
 Cannizzaro's reaction, **165**, 257, 330, 505, 759, 883, 915, 916
 Cantharidin, 692*
 Capri blue, 621
 Capric acid, 33, 193*, 203, 215, 217
 Capric aldehyde, 160*
 Caproic acid, 29, 193*, 194*, 203, 215, 682
 —, octyl ester, 211
 Caproic aldehyde, 160*
 Caproic anhydride, 222*
 Capronic acid, see Caproic acid
 Capronone, 174*
 Caproyl chloride, 221*
 Capryl chloride, 221*

- Caprylic acid, 193*, 203, 217
 Caprylic aldehyde, 160*, 169
 Caprylyl chloride, 221*
 Capsanthin, 711
 Capsicin, 462
 Carane, 692, 695
 Carbamic acid, 230
 —, esters, 229, **230**, 235
 —, salts, 230
 Carbamic acids, substituted, 470
 Carbamyl chloride, 230
 Carbanilide, 470*
 Carbazole, 384, 629, 788*
 Carbenium, formulation, 608
 Carbethoxy-*isovanillic* acid, 877
 Carbides, 27, 68–71
 Carbinol bases, 562, 607
 Carbinols, alkyl, 81
 Carbobenzoxychloride, 297
 Carbocyclic compounds, 373, 637
 Carbodiphenylimide, 471
 Carbohydrates, **321**, 906
 —, metabolism of, 320
 Carbolic acid, see Phenol
 Carbolines, 897
 Carbolineum, 384
 Carbon, 3
 —, detection of, 3
 —, estimation of, 5
 —, isotopes, 916
 —, micro estimation of, 10
 —, tervalent, 175
 —, valency, 21
 —, —, bond equivalence, 15
 —, —, bond equivalence electronic conception, 62
 See also double bond
 Carbon dioxide, 3
 Carbon disulphide, **229***
 Carbonic acid, 3, 190
 —, esters, 229
 Carbonium-salts, 401, 484, 562, **607**, 634, 708
 Carbon monoxide, 3, 15
 Carbon oxysulphide, 229*
 Carbon suboxide, 181*, 278
 Carbon tetrabromide, 228*
 Carbon tetrachloride, 32, 100, 182, **227***
 Carbon tetrafluoride, 228*
 Carbon tetraiodide, 228
 Carbonyl chloride, see phosgene
 Carbonyl form, 109
 Carbonyl group, 65, 160, 174
 Carbonyl-methylene, 180
 Carbostyryl, 814*
 δ -Carboxy-butyl-thiophen, 737
 α -Carboxycinchomeric acid 811*, 876
 Carboxyl group, 190
 Carboxyl-polypeptidase, 307
 Carboxylase, 90, 92, 291
 Carboxylic acids, alicyclic, 646, 650, 656, 689
 —, aliphatic, dibasic, 258, 273, 639, 640, 641, 749
 —, —, monobasic, 28, 33, 86, 117, 159, 187, **190**, 269, 913
 —, aromatic, 453, 503, 509, **521**, 525, **529**
 α -Carboxyphenylthioglycolic acid, 477, 767
 γ -Carboxypimelic acid, 672
 Carbylamines, 189
 Carbylaminereaction, 132, 454
 Cardiazole, 804
d-Carene, 672, 696
 Carius' method of analysis, 8
 Carminic acid, 598
 Carnegine, 875
 Carnosine, 299
 Carolic acid, 761
 Carolinic acid, 761
 Carone, 672, 686, **695***
 Caronic acid, 648*, 696
 Carotenes, 708, 709*, 728, 778
 Carotenoids, 708
 Carr and Price's reaction, 728
 Carrier substance, 731
 Carthamin, 520
 Carvacrol, 433*, 661, 685
 Carvacrol-phthalein, 434
 Carvenone, 696
 Carvestrene, **672**, 696
 Carvomenthol, 678
 Carvomethone, 683
 Carvone, 433, 661, 671, 674, **684***
 Carvotanacetone, 685, 694
 Caryophyllene, 707
 Casein, 288, 305, 308
 Castanitol, 315*
 Castoreum pigments, 553
 Catechins, 434, 545, **566***, 567*
 Catechol, see Pyrocatechol
 Caoutchouc, 739
 Cedrene, 707
 Cedriret, 581
 Cellite, 364
 Cellobiose, **354***, 367
 Cellohexaose, 363*
 Cellon, 364
 Cellotetraose, 363*
 Cellotriose, 363*
 Cellulases, 368
 Celluloid, 364, 702
 Cellulose, 93, **362**, 367, 485
 —, acetates, 364, **367**
 —, fermentation, 33
 —, methyl ether, 364
 —, nitrates, 364, 367
 —, xanthate, 364, 368
 Cephæline, 903
 Cerebron, 219
 Ceresin, 26, 41
 Cerotene, 58*
 Cerotic acid, 108, **203**, 213
 —, cetyl ester, 213
 —, myricyl ester, 213
 Ceryl alcohol, 108
 Cetene, 121
 Cetraric acid, 542
 Cetyl alcohol, 108
 Cetyl bromide, 74*
 Cetyl chloride, 74*
 Cetyl-ethyl sulphide, 121
 Cetyl iodide, 74*
 Cetyl palmitate, 213
 Cevadinic acid, 838
 Chain isomerism, 24
 Chain reaction, 79
 Chalkone, 516
 Chardonnet rayon, 367
 Chaulmoogric acid, 658*
 Chavibetol, 437*
 Chavicine, 851
 Chavicinic acids, 851
 Chavicol, 434*
 Cheirolin, 241
 Chelation, 520
 Chelidonic acid, 838
 Chicago blue, 494
 Chitin, 349
 Chitobiose, 349
 Chitosamine, see Glucosamine
 Chitosan, 349
 Chitose, 349
 Chloracetals, 266
 Chloracetic acid, **254***, 570, 574
 Chloral, 160, 181, **253***, 265, 417, 872
 Chloral alcoholate, 253*
 Chloral ammonia, 253
 Chloral hydrate, 162, 253*
 Chloranil, 579, **580***
 Chloretone, 178
 Chlorhydrins, 243, 244, 309
 Chlorides, acyl, 195, 211, **220**, 509, **522**

- See also Halides
- Chlorin, 582, 780
- Chloroacetaldehyde, 791
- Chloroacetone, 256
- Chloroacetonitrile, 762
- Chloroanilines, 463*
- Chlorobenzene, 293, 388, 414*
417
- p*-Chlorobenzene sulphonie acid, 426
- Chlorobenzoic acids, 533*
- Chlorobenzoquinones, 390, 579, **580***
- Chlorobutadiene, 741
- Chlorobutyric acid, 63*
- Chlorocarbonic esters, 229
- Chlorocarboxylic acids, 54
See also Halogen substituted acids
- Chlorocresol, 433, **444***
- Chlorocyclopropane, 645*
- Chloroform, 32, 100, 157, 176, **182***, 506, 914*
- Chlorogenic acid, **543***, 689, 690
- Chlorohydratropyltropine, 857
- 1-Chloro-2-iodoethylene, 416
- 1-Chloro-2-iodoethylethylene, 416
- 1-Chloro-2-iodoxyethylene, 416
- Chloroisoprene, 741
- α -Chloroketones, 261, 643, 644
See also Halogen substituted ketones
- Chloromalic acids, 283
- Chloromethyl-anisyl ketone, 841
- Chloromethyl benzenes, 418
- Chloromethyl-*p*-xylene, 745
- Chloronaphthalenes, 407
- Chlorophenols, 434, 437, **445***
- Chlorophyll, 111, 709, 768, 778
—, derivatives, 772
—, porphyrins, 38, 758–759
- Chlorephyll a, 778
- Chlorophyll b, 778, 780
- Chlorophyllin a, 778
- Chlorophyllin b, 778
- Chloroporphyrin **c**₆, 779
- Chloroprene, 741
- β -Chloropropionacetal, 850
- Chloropropionic acid, 254, 304
- Chloropropylenes, 64, 77
- Chloropyridines, 771, 807
- Chloropyridine dicarboxylic acid, 852
- Chloroquinoline, 785
- Chlororaphine, 617
- Chlorosuccinic acids, 254, 300, 304
- Chlorosulphonic acid, 112
- Chlorotetrahydrothiophens, 765
- Chlorothiophens, 765
- Chlorotoluenes, 392
- Cholanic acids, 710, 716, 717, 720, 725
- Choleic acid, 716
- Cholestane, 714
- Cholestenone, 714, 723
- Cholesterols, 213, **713***, 717, 720, 722, 723
- Cholic acid, 716, 717
- Choline, 218, **248**, 295
- Chondroitin sulphuric acid, 349
- Chondrosamine, 308, **349**
- Chondrosaminic acid, 349
- Chroman derivatives, 736
- Chrome dyes, 490, **491**
- Chromium organic compounds of, 155
- Chromoisomers, 465
- Chromone, 554
- Chromonols, 556
- Chromophores, 259, 404, **484**, 523, 574
- Chromotropic acid, **447**, 490
- Chrysamine, 493
- Chrysaniline, 633
- Chrysanthemin, 563
- Chrysanthemum carboxylic acid, 655
- Chrysarobin, 599*
- Chrysazin, 596
- Chrysene, 384, **412***, 714, 762
- Chrysin, 556*, 559
- Chrysoidine, 487
- Chrysophanic acid, 599*
- Chrysophenine, 494
- Ciba blues, 573
- Ciba red, see Thioindigo
- Ciba Scarlet, 575
- Ciba violets, 575
- Cibazole, 792
- Cincholoiponic acid, 866, 867, 869
- Cinchomeronic acid, 811*, 817, 876, 879
- Cinchonicine, 868
- Cinchonidines, 104, 865, **868***
- Cinchonines, 104, **866**, 868*, 869
- Cinchorinic acid, 814, 866, 870
- Cinchoninone, 866
- Cinchotoxine, 868
- Cineoles, **681***, 682*, 697
- Cinerolone, 655
- Cinnamic acids, 19, 402, **525***, 526*, 651, 912
- Cinnamic acids, esters, 79, **526**
—, *ortho*-substituted, isomerism, 397, 538
- Cinnamic alcohol, 255, **451***
- Cinnamic aldehyde, 507*
- Cinnamyl-cocaine, 862*
- Cinnamyl-tropeine, 857
- Cinnoline, 818
- Cinnoline methiodide, 818*
- Cis-trans isomerism, (carbon compounds), 48, 282, 526, 538, 608, 851
—, ring compounds, 647, 650, 657, 663, 692, 715
—, ring fusion, 408, 631, 715, 813, 856, 860
- Citraconic acid, 284*
- Citral, 110, **171***, 198
- Citric acids, 1, 284, **319***, 320, 690, 766, 838, 906, 917, 929
- Citric acid cycle, 320
- Citronellal, **170***, 684
- Citronellic acid, 208*
- Citronellol, **109***, 923
- Citronine A, 449
- Civetones, 751
- Claisen condensations, 267, 525, 662
- Clavatol, 517
- Clemmensen reduction, 392
- Cleve acids 447, 467
- Clupadonic acid, 215
- Clupein, 308
- Coal, 43, 383
—, world production, 930
—, world reserves, 930
- Coal-gas, 383
- Coal-tar, 383, 786, 788, 812, 816
- Coal-tar compounds, 922–927
- Cocæthylene, 861
- Cocaines, 768, 838, 859*, 861, 907
—, derivatives, 861
—, substitutes, 248
- Coccarboxylase, 92, 730
- Cochenillic acid, 598
- Cochineal dyes, 598
- Codehydrases, 360, 731
- Codeines, **888**, 891*
- Codeinones, 888, 890, 892*, 893

- Coelestine blue, 623
 Co-enzyme, 731, 733
 Coerulein, 636
 Coerulignone, 581
 Co-ferment, hydrogen carrying, 731
 Colamine, 219, 244, **248***, 530
 Colchicine, 895
 Colchicine, 838, **895**
 Colchinol, 895
 Collagen, 308
 Collidine, 788, 809
 β -Collidine, 868, 872
 Collidine dicarboxylic acid, 809
 Collodion, 364
 Colour, theory of, 484
 Combustion, heats of, 750
 Compensation, intermolecular, 107
 —, internal (= intramolecular), 107, 663
 Conduritol, 677
 Configuration, absolute, 333
 Conglomerate, 102
 Congo red, 492, **493**
 Conhydrines, **848***, 907
 Coniceines, 847*, 907
 Coniferin, **508**, 540
 Coniferyl alcohol, 436
 Coniine, 846*, 907
 Conjugation, 58, **59**, 65, 653, 748
 Constitutional formulæ, 14
 Convolamine, 858*
 Convolvine, 857
 Conyrrine, 846
 Coordination compounds, 186
 — number, 186
 — valency, 126
 Copæne, 707
 Copper phenyl, 155
 Coprostan, 716
 Coprosterols, 715, 716, 722
 Coramine, 811
 Coronene, 413
 Corpus luteum hormones, 720
 Corrosive gases and vapours, 936
 Corticosterone, 724
 Corybulbines, 887
 Corydaline, 887
 Cotarnic acid, 879
 Cotarnine, 879, 882*, 883, 885
 Cotoin, 518*
 Cotton, 362, 487
 —, production, 937
 Coumalic acid, 550
 Coumalin, 550*
 Coumaran, 761, 762
 Coumaric acid, 284, 526, **538***
 Coumarilic acid, 761
 Coumarin, 526, **538***, 761, 762
 Coumarin derivatives, 551
*iso*Coumarin derivatives, 552
 Coumarinic acid, 284, **538**
 Coumarone, 755, **761**
 Coumarone resin, 762
 Coupling, 481
 Cozymase, 91, 731
 Cracking, 39, 42
 Creatine, 295, 918
 Creatine phosphoric acid, 295
 Creatinine, 295
 Creoline, 433
 Cresols, 292, 384, 433*, 609
o-Cresolsulphonic esters, 507
o-Cresotic acid, 491
 Croceine acid, 447
 Croceine scarlet 3 B, 489
 Crocetin, 712
 Crocetin-dimethyl esters, 713
 Crocin, 354, 712
 Croconic acid, 655, 656
 Crotonic acids, 170, 205, **207***, 284
 Crotonic aldehyde, 164, 170*
 Crotonoside, 345
 Crotyl *isothiocyanate*, 241*
 Cryptopine, **896***
 Crystal violet, 613
 Crystallose, 534
 Cumenes, 392*, **393***, 531
 Cumenols, 433
 Cumidine, 458
 Cumotocopherol, 736
 Cumulenes, 59
 Cuprammonium rayon, 368
 Cupreine, 865, **874***
 Cuprene, 70
 Curare, 904
 Curcuma, 521
 Curcumin, 521*
 Curtius' reaction, **130**, 250, 453, 523, 689
 Cuscohygrine, **843***, 859, 906
 Cyamelide, 235
 Cyanacetic acid, 277
 —, ester, 278
 Cyanacetyl chloride, 852
 Cyanalkines, 189, 819
 Cyanamide, 231, **236**
 Cyanamides, alkyl, 236
 Cyanates, **235**, 523
*iso*Cyanate esters, 128, 130, **235**, 470, 479
 Cyanhydrins, **160**, 285, 332, 548
 Cyanic acids, **235**, 263
 Cyanides, alkyl, 84, 129, 185, 249, 749, 819
 —, aryl, 425, 478, 510, 514, 527
 —, complex, 186
 —, metallic, 185–7
*iso*Cyanides, 132, 185, 187, **189**
 Cyanidin, 563, 564, 566
 Cyanin, 563
 Cyanine blue, 815
 Cyanine dyes, 815
*iso*Cyanine dyes, 815
 Cyanmethine, 819
 Cyanoacetamide, 732
 Cyanoacetic ester, 825, 829
 Cyanobenzamide, 788
 Cyanoformic ester, 835
 Cyanogen, 2, 18, **272***, 383
 Cyanogen bromide, 235*, 524
 Cyanogen chloride, 235*
 Cyanogen iodide, 236*
 Cyanoquinoline, 867
 Cyanosin, 636
 Cyanuric acids, 235, **237**, 835
 —, esters, 235, 237, 835
 Cyanuric amide, 237
 Cyanuric chloride, 237, 835
 Cyaphenine, 524, 835
 Cyclamin, 564
 Cyclic hemiacetals, 256, 323, 339
 Cycloacetals, 255
 Cyclobutadiene, 649
 Cyclobutane, 57, 641, **649***, 750
 Cyclobutane carboxylic acid, 650*
 Cyclobutane derivatives, 641, 649
 Cyclobutanedi carboxylic acids, 650*, 651
 Cyclobutanol, 643, **650***
 Cyclobutanone, 650*
 Cyclobutene, 649
 Cyclobutylamine, 643, 650
 Cyclobutylcarbinol, 644, **650**
 Cyclobutyl-methyl ketone, 650*
 Cyclobutylmethylamine, 644
 Cyclodecanone, 750*
 Cyclododecanone, 750*
 Cycloheptadecamethylene, 750
 Cycloheptadecanone, 750*, 751
 Cycloheptadiene, 642, 742, 744*
 Cyclohexane, 642, **742**, 744*
 —, derivatives, 742

- Cycloheptane carboxylic acid, 744
 Cycloheptanol, 742
 Cycloheptanone, 275, 742*
 Cycloheptatriene, 742, 744*, 855
 Cycloheptatriene carboxylic acid, 744
 Cycloheptene, 742, 744*
 Cycloheptyl bromide, 742
 Cyclohexadecanone, 750*
 Cyclohexadienes, 578, 662, **668***
 Cyclohexane, 39, 386, 389, 641, 642, **665***, 750
 Cyclohexane derivatives, 659
 —, stereoisomerism of, 663, 692
 Cyclohexane, polyhydroxy compounds, 662, 675
 Cyclohexane carboxylic acids, 665, 689, 692
 Cyclohexanediols, **674***, 690
 Cyclohexanedione, 662, 665
 Cyclohexanehexaone, see Triquinoyl
 Cyclohexane-triols, 674*
 Cyclohexanol, 280, 385, 666, **674***
 Cyclohexanone, 275, 280, 385, 631, 640, 665, **682***
 Cyclohexanone carboxylic acids, 639, 691
 Cyclohexatriene, see Benzene
 Cyclohexene, 385, 662, **666***
 Cyclononadecanone, 751
 Cyclononanone, 748, 749, 750*
 Cyclooctadecanone, 750*
 Cyclooctadienes, 746, 748*
 Cyclooctane, 641, 742, **746**, 748*
 —, derivatives, 746
 Cyclooctanone, 275, 746, 749, 750*
 Cyclooctatetraene, 747*, 748*, 863
 Cyclooctatriene, 746, 748*, 863
 Cyclooctene, 748*
 —, derivatives, 746
 Cyclopentadecamethylene, 750
 Cyclopentadecanol, 751
 Cyclopentadecanone, 264, 750*, 751
 Cyclopentadiene, 383, **653***
 Cyclopentane, 39, 641, **652***, 750
 Cyclopentane carboxylic acid, 643, **657***
 Cyclopentanedicarboxylic acids, 657*
 Cyclopentanepentaone, 655
 Cyclopentanol, 644, 654
 Cyclopentanone, 275, 640, 652, **654***
 Cyclopentanone carboxylic acid, 639
 Cyclopentene, 644, **653***
 Cyclopenteno-benzanthracene, 411
 Cyclopentenophenanthrene derivatives, 719
 Cyclopropane, 242, 641, **645***, 750
 Cyclopropane carboxylic acid, 639, 646*
 Cyclopropanedi carboxylic acids, 646, 647*
 Cyclopropanetri carboxylic acids, 646, 647, 744
 Cyclopropanone, 646
 Cyclopropene, 645*
 Cyclopropylamine, 645
 Cyclopropylcarbinol, 643
 Cyclopropylmethylamine, 643
 Cyclopropylmethyl-ketone, 646*
 Cyclotetradecanone, 750*
 Cyclotridecanone, 750*, 751
 Cyclotrimethylene-imine, 250
 Cyclotrimethylene-trinitramine, 167, 168
 Cycloundecanone, 750*
 Cymarin, 726
 Cymarose, 345, 726
m-Cymene, **394***, 672
p-Cymene, **394***, 637, 662, 666, 670
 Cysteine, 247, 286, 288, 293, 302
 Cystine, 286, 288, 289*, 787
 Cytidine, 830, 832
 Cytidylic acid, 830, 832, 833
 Cytisine, 903
 Cytochromes, 731, 776
 Cytosine, 819, **820**, 830
 D-form, series, 105
 d (= dextro) form, 99
 Dagenan, 808
 Dahl's acids, 467
 Dahlia B, 613
 Daidzein, 560
 Daidzin, 560
 Damascenin, 535*
 Dambonitol, 676
 Daphnetin, 552*
 Daphnin, 552
 Dative bond, see Semi-polar
 D.D.T., 417
 Decahydroanthracene, 410
 Decahydronaphthalene or decalin, 407
 Decahydro- β -naphthols or decalols, 408*, 742
 Decahydroquinolines, 813*
 Decane, 23, 30*
 Decane dicarboxylic acid, 274*
 Decarboxylase, 733
 Decoses, 347
 Decyl alcohol (prim.), 85*
 Decylamine, 131*
 Dehydracetic acid, 804
 Dehydroandrosterone, 722, 723
 Dehydroascorbic acid, 734
 Dehydrocamphoric acid, 701
 7-Dehydrocholesterol, 735
 Dehydrocorydaline, 887
 Dehydrogenation, 86, 682, 707, 714, 898
 Dehydrogeranic acid, 210*
 Dehydroindigo, 573
 Dehydromucic acid, 758, 760
 Delphine blue B, 623
 Delphinidin, 563, 564
 Delphinin, 563
 Deoxycholic acid, 716, 717
 Deoxycorticosterone, 724
 Depsides, **540**, 545
 Depsidones, 542
 Dermatol, 544
 Derric acid, 764
 "Des" compounds, 743
 Desmotropism, **109**, 139, 316
 Desoses, 830
 Desoxybenzoin, 515*
 Desoxyleucopterins, 833, 834
 Desoxy-sugars, 830
 Deuterium compounds, 911
 Deuteroacetic acids, 914*
 Deuteroacetylene, 912
 Deuterobenzenes, 912, 914*
 Deuterocamphanes, 912, 915
 Deuteriochloroform, 914*
 Deuterohydroxybutyric acid 197
 Deuteromethane, 912
 Deuteroporphyrin, 775
 Deuteropropionic acids, 915
 Deuteriosuccinic acids, 912, 914*
 Deuteroxyl compounds, 912
 Dextrins, 358, 359
 Dextro, see d-form
 Dextrose, 337
 Diacetonyl alcohol, 176

- Diacetyl, **258***, 378, 578, 662
 Diacetyl peroxide, 223*
 Diacetylacetoacetic acid, 804
 Diacetyldeuteroporphyrin, 775
 Diacetylsuccinic acid, 261
 Diacyl peroxides, 29, **222**
 Dial, 79, 279
 Dialdehydes, **257**, 640
 Diallyl, 58
 Diallyl disulphide, 120
 Diallyl ozonide, 258
 Dialuric acids, 315, 824, 825
 Diamine black B.H., 493
 Diamine golden yellow, 494
 Diamine pure blue, 494
 Diamine pure blue FF, 494
 Diamines, aliphatic, 249
 —, aromatic, **458**, 583, 656, 801
 Diaminoacetone, 795
 Diaminoazoxybenzene, 493
 Diaminoazoxytoluene, 494
 Diaminobutane, 251*, 771
 Diaminobiphenyl, 788
 Diaminogen blue BB, 494
 Diaminohexane, 251
 Diaminonaphthalenes, 461*
 Diaminophenazines, 458, 616
 Diaminophenol, 448
 Diaminophenthiazines, 624
 Diaminopropionic acid, 302
 Diaminopyridines, 808
 Diaminostilbene, 784
 Diaminostilbenedisulphonic acid, 492
 Diaminouracil, 825, 827
 Diamond black F, 491
 Diamond black PV, 492
 Diisoamyl ether, 119*
 Diamyl ketone, 174*
 Dianilinohydroquinone, 577
 Dianilinoquinone, 577, 586
 Dianilinoquinone-dianil, 577
 Dianisidine, **492**, 495.
 Diastase, 93, 353, 358
 Diastereoisomerism, 48, 102
 Diazines, 656, **817**
 Diazoacetic ester, 294*, 387, 647, 744, 745, 770, 796, 836
 Diazoacetophenone, 522
 Diazoacids, 293
 —, esters, 293, 294
 —, amides, 294
 —, nitriles, 294
 Diazoamino compounds, 472, **481**
 Diazobenzene amine, 479
 Diazobenzene imine, 479
 Diazobenzene sulphonic acid, 466
 Diazo compounds, aliphatic, 293, 522, 836
 —, aromatic, 476, 818
 Diazo cyanides, 476
 Diazohydrates, 475
 Diazoic acids, 475
 Diazoketones, 193, 770
 Diazomethane, 193, **294***, 440, 644, 646, 796
 Diazonium bases, 131, **475**
 Diazonium perhalides, 474, 479
 Diazonium salts, 427, **472**, 481, 501, 770
 —, double compounds, 474, 479, 496
 Diazonium xanthates, 477
 Diazo oxides, 473, 482
 Diazo-reactions, 476
 Diazo sulphides, 473
 Diazo sulphonates, 480
 Diazotates, **475**, 495
 Diazotization, 472
 Dibenzalacetone, 516*
 Dibenzanthracene, 411
 Dibenzenyl azoxime, 515
 Dibenzo- α -pyrone, 551, **553**
 Dibenzo- γ -pyrone, see Xanthone
 Dibenzoyl peroxide, 522*
 Dibenzoylpyrene, 602
 Dibenzpyrenequinone, 602
 Dibenzyl chlorophosphonate, 831
 Dibenzyl ether, 503
 Dibiphenylene-ethylene, **404**, 654
 Dibromoacetoacetic ester, 760
 Dibromoadipic ester, 281
 Dibromobehenic acid, 255
 Dibromobenzenes, 417
 Dibromobutanes, 241, 242, 645
 Dibromobutenes, 60*
 Dibromoethane, 53, **242***, 280, 646, 651
 Dibromofuran, 758
 Dibromomenthane, 670
 Dibromopentane, 241, 242, 652
 Dibromopropane, **242***, 639, 645, 649
 Dibromopropionaldehyde, 739
 Dibromopyridine, 808
 Dibromoresorcinol dimethyl ether, 389
 Dibutyl ether, 116*
 Dibutyl ketone, 174*
 Diisobutylene, 56
 Dicaproyl peroxide, 29
 Dicarboxylic acids, saturated see Carboxylic acids
 Dichlorhydrins, 309
 Dichloroacetic acid, **254***, 265, 833
 Dichloroacetylene, 78*
 Dichloroaniline, 463
 Dichlorobenzenes, 416, 417*
 Dichlorobutanes, 61, 242*
 Dichlorodiphenyl(trichloromethyl) methane, 417
 Dichloroethanes, 158*, 242*
 Dichloroethylenes, 49, 70, 252*
 Dichloromaleic acid, 580
 Dichloromenthane, 678
 Dichloromethane, 32, 100, **158***
 Dichloronaphthaquinone, 405
 Dichloropentane, 242
 Dichloropropanes, 105, 158*, 242*
 Dichloropropionic acid, 266
 Dichlorosuccinnic acid, 254
 Dicinnamylidene-acetone, 516*
 Dicoumarol, 552
 Dicyandiamide, 236
 Dicyanogen, 272
 Dicyclopentadiene, 653*
 Dideuterobutyric acids, 197
 Dideuteroethylene, 915
 Dideuterohydrocinnamic acid 912
 Diels' hydrocarbon, 714
 Diene synthesis, 60, 654
 Diethyl ether, 116*, **118***
 Diethyl ketone, 174*
 Diethyl peroxide, 119
 Diethyl sulphate, **113***
 Diethyl sulphide, 121*
 Diethylacetal, 886
 Diethylamine, 281
 Diethylamino-propionic ethyl ester, 281
 N-Diethylaminoethyl alcohol, 248
 Diethylcarbinol, 914*
 Diethylenediamino-pæronol cobalt salts, 519
 Diethyllucine ester, 248
 Diethyllucinol, 248
 Diethylurea, 231
 Diformylhydrazine, 137
 Digallic acid, 545*
 Digitalis glucosides, 724
 Diginose, 345

- Digitalose, 345
 Digitogenin, 727
 Digitonin, 104
 Digitoxigenin, 725, 726
 Digitoxin, 725
 Digitoxose, 725
 Diglycolic acid, 262
 Digoxigenin, 726
 Dihexyl ketone, 174*
 Dihydroandrosterone, 722, 727
 Dihydroanthracene, 410
 Dihydrocarveol, 671, 685
 Dihydrocarvone, 685, 686
 Dihydrocarvone hydrobromide, 686, 696
 Dihydrocholesterols, 715, 720, 722
 Dihydrocivetol, 751
 Dihydrocivetone, 751
 Dihydrocrocin, 712
 Dihydroergosterol, 735
 Dihydrocupreine ethers, 874
 Dihydronaphthalene, 407
 Dihydropseudoionone, 705
 Dihydropyrazines, 821
 Dihydroquinine, 872
 Dihydroquinotoxine, 872
 Dihydroresorcinol, 437, 661
 Dihydrotachysterol, 735*
 Dihydrotetrazine dicarboxylic acid, 836
 Dihydrouracil, 818, 819
 Dihydroxyacetone, 310, 342, 344
 Dihydroxyacetone phosphate, 90, 360
 Dihydroxybiphenyl, **428**, 581
 Dihydroxybromobenzoic acids, 544
 Dihydroxydiethylstilbene, 720
 Dihydroxydimethylbutyrolactone, 737
 Dihydroxyethyl peroxide, 118
 Dihydroxymaleic acid, 255, 318
 Dihydroxymalonic ester, 834
 Dihydroxynaphthalenes, 443*
 Dihydroxyphenanthrene, 764
 Dihydroxy-phenazine-di-N-oxide, 617
 Dihydroxyphenylalanine, 288, 289*, 303
 Dihydroxypyrimidines, 818, 819
 Dihydroxyquinoline, 644
 Dihydroxyisoquinoline, 644
 Dihydroxytartaric acid, 490
 Dihydroxytropone, 859
 Diiodotariric acid, 255
 Diiodotyrosine, 287
 Diketones, 243, **257**, 429, 459, 555, 640
 α -Diketones, 257, 267, 515, 578, 793, 834
 β -Diketones, 259, 791, 796, 818
 γ -Diketones, 261, 757, 768
 Diketopiperazines, 297, 821
 Dimercaptal, 120
 Dimethoxyisoquinoline, 876
 Dimethoxyisoquinoline carboxylic acid, 876
 Dimethylacetoacetic ester, 271
 Dimethyl acetylene, 394
 Dimethylallene, 59
 Dimethylamine, **133**
 Dimethylaminoazobenzene, 482
 Dimethylaminoethyl-dimethoxybenzaldehyde, 896
 N-Dimethylaminophenol, 468*, 633
 o-(2-Dimethyl-aminophenyl)-phenyl-trimethyl ammonium iodide, 396
 2:5-Dimethyl-4-aminopyrimidine, 729
 Dimethylaniline, **455***, 461, 488, 610, 613, 624
 Dimethylaniline oxide, 456*
 Dimethyl arsine, 144*
 Dimethylarsine chloride, 144
 Dimethylbutadiene, 61, **62**, 483, 741
 Dimethylbenzophenone, 511
 Dimethylbutanes, 25, 31*
 Dimethylbutylbenzene, 394*
 Dimethyl carbonate, 229*
 N-Dimethylcolamine, 248
 Dimethylcyclohexane, 665*
 Dimethylcyclopentane, 642, 742
 Dimethylcyclopentane-1-carboxylic acids, 657*
 Dimethylcyclopropane, 641, 645*
 Dimethylcysteine, 792
 Dimethyl-dibenzylammonium bromide, 134
 Dimethyl-diethyl methane, 146*
 Dimethyl-diethyl silane, 146*
sym-Dimethyl-diphenyl-urea, 470*
 Dimethylenecyclohexadiene, 747
 Dimethyl ether, 116*, 118
 Dimethyl-ethyl-*isobutyl* silane, 146*
 Dimethylethylene glycol, 247*
 Dimethyl-ethyl-methane, 15
 Dimethyl-ethyl-phenyl methane, 146*
 Dimethyl-ethyl-phenyl silane, 146*
 Dimethyl-ethyl-propyl silane, 146*
 Dimethylfulvene, 653
 Dimethylfuran, 261, 757
 Dimethylglyoxime, 259
 —, metallic complexes, 259
 Dimethylhexadiene dicarboxylic acid, 198
 Dimethylketene, 180
 Dimethylketol, 257*
 Dimethylmalonic acid, 440, 532, 709
 2:6-Dimethyl-4-methoxy-pyridine, 805
 Dimethyl oxalate, 88
 Dimethylpentanes, 35*
 Dimethylphenanthrene, 718, 725
 Dimethylphenanthrol, 718
 Dimethylphenylene diamine, 461
 Dimethylpolysiloxane, 147
 Dimethylpropanol, 97*
 Dimethylpropyl-acetamide, 129
 Dimethylpyrone, 131, 804, 805*
 Dimethylpyrrole, 261
 Dimethylquinolines, 793
 Diethylquminone, 578, 662
 Dimethyl stannone, 149
 Dimethyl sulphate, **113***
 Dimethyl sulphide, 121*
 Dimethyl sulphone, 123
 Dimethylthiophens, 261, 766*
 Dimethyltriazole, 781
cyclic Dimethyltrisiloxane, 147
 Dinicotyl-ornithine, 293
 Dinitraniline, **465***, 473
 Dinitrobenzenes, **419**, 420, 421*, 460
 Dinitrobiphenyl, 817
 Dinitrobiphenyl dicarboxylic acid, 395
 Dinitrochlorobenzene, 415, 427
 Dinitrocresol, 449*
 Dinitrohydroxynaphthalene, 449
 Dinitromethane, 141
 Dinitrophenols, 420, 427, 429, **448***

- Dinitrosoresorcinol, 582
 Dinitrostilbene, 420
 Dinitrotoluenes, 419, 420, 421*
 Dioctyl ketone, 174*
 Dionin, 892
 Diorsellinic acid, 312
 Diosmetin, 557
 Diosmin, 557
 Diosphenol, 687*
 Dioxane, 246*
 Dioximes, 800
 Dioxindole, 784
 Dioxopiperazines, 821
 Dipentene, 669, **670**, 740
 Dipentene tetrabromide, 672*
 Dipeptidases, 307
 Dipeptides, 297, 821, 822, 901
 Diphenic acid, 531, 590
 Diphenoquinone, 581
 Diphenyl disulphide, 426
 Diphenyl ether, 432
 Diphenylacetylene, 403*
 Diphenylamine, 430, **456***, 614, 630, 788
 —, nitroderivatives, 465
 Diphenylamine blue, 614
 Diphenylamino radicals, 499
 Diphenylbenzidine, 456
 Diphenylbenzidine disulphonate, 396
 Diphenyl-biphenylene-ethylene, 404
 Diphenylbromomethane, 401
 Diphenylcarbinol, 399
 Diphenylcyclobutane dicarboxylic acids, 636
 Diphenyl-dichloro-methane, 404
 Diphenyl-di- α -naphthylallene, 690
 Diphenylene oxide, 745*
 Diphenylethane, 399*
 Diphenylethylene, see Stilbene
 Diphenylfulvene, 653
 Diphenylguanidine, 471
 Diphenylene, 498
 Diphenylene rearrangement, 498
 Diphenyliodonium-hydroxide, 416
 Diphenylmethane, 398*
 Diphenylmethyloide, 551, **553**
 Diphenylnaphthylallene carboxylic acid, 690
 Diphenylquinomethane, see Fuchson
 Diphenylsilanediol, 147
 Diphenyltetraketone, 516*
 Diphenylthiourea, **470***, 571
 Diphenyltriketone, 516*
 Diphenylurea, 470*
 Dipole, 63
 Dipropyl ethers, 116*, 119
 Dipropyl ketone, 174*
 Dipropyl sulphide, 121*
 Dipterine, 841
 Direct deep black, 493
 Dipyrrolyl compounds, 774
 "Direct" effect, 63, 416
 Disiloxane, 147
 Disproportionation, 662
 Dissociation constants of organic acids, 194, 206, 274, 915, 940
 Dissociation constants of organic bases, 939
 Distannanes, 149
 Distyrene, 403
 Disulphides, alkyl, 120
 Dithio acids, 195
 Dithiobenzoic acid, 523
 Dithiocarbamic acids, 132
 Dithiocarbonic acid, 230
 Dithioformic acid, 792, 826
 Diuretin, 828
 Divarinol, 542
 Divi-divi, 547
 Divinylacetylene, 69
 Dixanthogenes, 230
 dl (= i) form, 102
 Döbner's violet, 610
 Döbner and Miller's synthesis, 812
 Docosane, 30*
 Dodecane, 30*
 Dodecyl alcohol, 85*, 108
 Dodecylaldehyde, 160
 Dodecylamine, 131*
 Dodecylene, 51
 Dohexacontane, 29, 37*
 Doisynolic acid, 720
 Dotriacontane, 30*
 Double bond, 46, 62
 —, conjugated, 58, 59, 65, 653
 —, cumulative, 58
 —, oscillating, 378, 807
 —, semicyclic, 667, 670, 684
 Drying acids, 209
 Drying oils, 213
 Dulcine, 470*
 Dulcitol, 114, 314*, 339
 Duprene, 741
 Durenes, **394***, 579
 Dye base, 607
 Dyes and colour, 484
 Dynamite, 310
 Ecgonines, 859, 860, 907
 Ecgoninic acid, 783, 854, 859, 860
 Echinochrome A, 589
 Eclipse blue, 628
 Edestin, **288**, 307
 Effect, direct, 63
 —, general, 63
 —, induced, 63
 Eicosane, 30*
 Eicosane carboxylic acid, 203
 Eicosane dicarboxylic acid, 281
 Eicosane tetraenoic acid, 215
 Elaeostearic acid, 209*
 Elaidic acid, 208*
 Elaidinisation, 215
 Elastin, 308
 Electrical combustion furnace, 11
 Electromers, 64
 Electron, lone pair, 65
 Electrophilic atom, 64
 Electrophilic substitution, 388
 Elementary analysis, 3, 5
 Elemicins, 439*
 Ellagic acid, 553
 Emeraldine, 585
 Emetine, 903
 Emodin, 599
 Empirical formulæ, 11
 Emulsin, 184, **328**, 355, 548
 Enantiomorphism (= enantio-stereoisomerism), 99, **101**, 107, 134
 Endoimino compounds, 803
 Enol form, 109, 913
 Enolase, 91
 Enzymes, 90, 776
 —, proteolytic, 306
 —, glycosidic, 350
 Eosin, 636
 Ephedrine, 463, 839*, 905
 Epichlorhydrin, 309
 Epimerism, 329
 Epoxides, 711
 Equilenin, 718*, 719, 723
 Equilin, 718*
 Erepsin, 298, **307**
 Ergine, 900
 Ergobasine, 900, 901
 Ergobasine, 900
 Ergocornine, 900
 Ergocorninine, 900
 Ergocristine, 901, 901
 Ergocristinine, 900
 Ergocryptine, 900
 Ergocryptinine, 900
 Ergometrine, 900, 901

- Ergometrinine, 900
 Ergonovine, 900
 Ergosine, 900
 Ergosinine, 900
 Ergosterol, **716**, 735
 Ergostetrine, 900
 Ergot alkaloids, 900
 Ergotamine, 900, 901
 Ergotaminine, 900
 Ergotocine, 900
 Ergotoxine, 900
 Eriochrome black T, 492
 Eriochrome blue-black B, 492
 Eriochrome red B, 799
 Eriodictyol, 559
 Erucic acid, 205, **208***, 284
 Erysoline, 241
 Erythrene, see Butadiene
 Erythrin, 312, 541
 Erythritols, 114, **311***, 334
 Erythrose, **334**, 336, **344**
 Erythrosin, 636
 Erythrulose, 312, 344
 Eserine, 903
 Eseroline, 903
 Essential oils, 191, **638**, 759
 Esters, 74, 81, 82, 192, 195, **210**, **431**, 450, 639
 Ester phosphatides, 218
 Esterification, **73**, 87, 111, **431**, 522, 527, 917
 Estragole, 434*
 Ethane, 23, 27, 30*, **34**
 Ethane tetracarboxylic acid, 278
 Ethanolamine, see Colamine
 Ether, see Diethyl ether
 Ethers, 51, 54, **115**, 126, 212, **430**
 Etherin theory, 18
 Ethoxyacetylacetone, 732
 Ethoxypropiosyringone, 366
 Ethoxypropioveratrone, 366
 Ethoxytryptophane, 900
 Ethyl, 150
 Ethyl acetate, 211*, **212**
 Ethyl acetoacetate, see Acetoacetic ester
 Ethyl alcohol, 1, 72, 73, 81, 84, 85*, **88**, 265, 366, 913
 Ethyl benzoate, 95
 Ethyl bromide, 74*, 76
 Ethyl butyrate, 211*
 Ethyl carbamate, 230
 Ethyl carbonate, 182, 229*
 Ethyl chloride, 74*, 76
 Ethyl chlorocarbonate, 229*
 Ethyl cyanides, 188*, 189
 Ethyl fluoride, 77*
 Ethyl formate, 94, **211***
 Ethyl hypochlorite, 112*
 Ethyl iodide, 74*
 Ethyl iodochloride, 416
 Ethyl mercaptan, 85, **119***
 Ethyl nitrite, **112**, 138*, 472
 Ethyl nitrobenzoate, 95*
 Ethyl oenanthate, 211*
 Ethyl orthoformate, 183, **220***
 Ethyl pelargonate, 211*
 Ethyl phosphate, 114*
 Ethyl red, 816
 Ethyl silicates, 114*
 Ethyl sulphite, 113*
 Ethyl isovalerate, 211*
 Ethylacetanilide, 469
 Ethylacetylene, 67
 Ethylamine, 131*
 Ethylbenzene, 391, 392*, **393**, 402
 Ethylboric acid, 151*
 N-Ethyl-carbostyryl, 793
 O-Ethyl-carbostyryl, 793
 Ethylene, 18, 42, 44, **57***, 383, 384, 391
 Ethylenes, 39, **43**, 133, 402, 523, 641
 Ethylenes configuration, 47
 Ethylenes nomenclature, 49
 Ethylenes structure, 44
 Ethylene chlorhydrin, 244
 Ethylene dibromide, 53, **242***, 280, 646, 651
 Ethylene dichloride, 242*
 Ethylene dithioglycol, 247
 Ethylene glycol, 45, 243, **246***, 265
 Ethylene lactic acid, 263
 Ethylene oxide, 244*, 450
 Ethylene thioglycols, 247
 Ethylenediamine, 250, 251*
 Ethyleneimine, 251*
 Ethylidene chloride, 158*
 Ethylidene diacetate, 222
 Ethylidene lactic acid, see Lactic acid
 Ethylidene peroxides, 118
 Ethyl-methyl-acetylene, 67
 Ethylpentane, 35*
 Ethyl-propyl ethers, 295
 Ethylpyrrolidine, 251
 Ethyl-quinuclidine, 868
 Ethylsulphonic acid, 116
 Ethyl-tetradeuteroethylcarbinol, 914*
 Ethyl-*pseudo*-thiourea, 820
 Ethyl-tricarballic acid, 901
 Ethyl-trimethyl-ammonium iodide, 134
 Eucaines, 861
 Eucalyptol, 681
 Eucarvone, 686*, 744*
 Eucupine, 874
 Eudalene, 706
 Eudesmol, 706
 Eugenols, 434, **435***, 436*, 508
 Euphorin, 231
 Euphthalmine, 858
 Eurhodines, 616
 Eurhodols, 616, 617
 Euxanthic acid, 347, 561
 Euxanthone, 347, 561*
 Evernic acid, 541*
 Evipan, 279
 Evodiamine, 899*
 Exalgine, 469
 Exaltol, 751
 Exaltone, 751
 Exhaustive methylation, 51, **133**, 385, 743, 746, 848, 854, 894
 F-acids or δ -acids, 447, 467
 Farnesol, 58, **110**, 705, 706
 Fast reds, 488
 Fast yellow G, **488**, 489, 799
 Fats, 17, 192, **213**, 716
 —, hardening of, 215
 Fatty acids, see Carboxylic acids
 Fehling's solution, **319**, 344
 Fenchenes, 704
*iso*Fenchocamphoric acid, 704
 Fenchocamphorone, 703
 Fenchones, 703*, 704
 Fermentation, see Alcoholic, Butyric, Lactic fermentation, etc.
 Ferments, see Enzymes
 Ferric ferrocyanide, 186
 Ferricyanic acid, 186
 —, salts, 186
 Ferrocyanic acid, 186
 —, salts, 186
 Ferulic acid, 543*
 Fibrinogen, 307
 Fibroin, 308
 Fichtelite, 412
 Filixic acid, 863
 Filmarone, 863
 Fischer-Tropsch-Ruhrchemie process, 43
 Fisetin, 557*
 Fittig's synthesis, **391**, 399
 Flavan derivatives, 566
 Flavanones, **555**, 559

- Flavanthrene dyes, 601
 Flavazine, 799
 Flavianic acid, 272
 Flavinduline B, 617
 Flavin phosphate, 731
 Flavins, 730
 Flavones, 554, **555***, 556, 565
*iso*Flavones, 560
 Flavonol, **556***, 565, 566
 Flavopurpurin, 597
 Flavoxanthin, 711
 Fluorene, 384, **398***, 404, 553, 653
 Fluorenone, 399
 9-Fluorenyl-trimethyl-ammonium hydroxide, 134
 Fluorescein, 635
 Fluorides, 77, 220
 Fluorobenzene, 414*
 Fluorobenzoic acids, 533
 Fluoroform, 184*
 Folic acid, 535, 739
 Follicular hormones, 717
 Formaldehyde, 88, 160*, **166**, 342, 418, 612, 631, 633, 905
 Formaldehyde-sodium-sulphoxylate, **168**, 502, 572
 Formalin, 166
 Formamide, 224*
 Formamide oxime, 238
 Formamidine, 826
 Formanilide, 469
 Formhydroxamic acid, 226*
 Formic acid, 17, 88, 159, 192, **194***, **198***, 630
 —, esters, 212
 —, salts, 159, **199**, 504
 Formononetin, 560
 Formose, 342
 Formylacetic ester, 798, 820
 Formyl chloride compounds, 221
 Formyl chloride, oxime, 238
 Formyl fluoride, 212
 5-Formylpyromucic acid, 760*
o-Formyltoluide, 784
 Frangula-emodin, 599*
 Frangula-emodin methyl ether 599*
 Fraxetin, 552*
 Free energy, 380
 Free radicals, 150, 399, 590
 Free rotation, **47**, 66
 —, restriction of, 396, 512, 771
 Friedel-Crafts synthesis, 391, 410, 510
 Friedländer's synthesis, 812
 Fructofuranose phosphates, 90
 Fructoses, 89, 329, **338**, 339, 343, 344, **346***, 352, 353, 355, 356, 357, 360, 917
 Fruit essences, 212
 Fuchsia, 619
 Fuchsin, 486, 609, **613**, 633
 Fuchsins, 605
 Fuchsin-sulphurous acid, **165**, 504
 Fuchsone, 605*
 —, hydroxy derivatives, 609
 Fuchsonimines, 606, 610
 Fucose, **345***, 357
 Fucoxanthin, 711
 Fulminic acid, 238
 Fulvenes, 404, 653
 Fumaric acid, 68, **281**, 283*, 320, 580, 838, 917
 —, dinitrile, 273
 Fumaric ester, 294, 647
 Fumaroid form, 282
 Fumaro-protocetraric acid, 542
 Fumigatin, 581
 Function, 72
α-Furaldehyde, 759*
 Furan, 755, **757**, 768
 Furan-*α*-carboxylic acids, 758, 759
 Furanoses, 324
 Furazans, 756, 800
 Furfural, 94, 330, 348, 441, 757, 758, 759*
 Furfuraldehyde, 759*
 Furfuroyl radical, 757
α-Furfuryl alcohol, 759*
 Furfuryl radical, 757
 Furil, 759
 Furilic acid, 759
 Furoin, 759
 Furoyl radical, 757
 Furylacrylic ester, 388
 Furyl radical, 757
 Fusel oil, 93, 759
 G-acid, 447
 Gabriel synthesis, 129, 247, 249, 285, **529**, 847
 Galactans, 346, 356, 362, 367
 Galactogen, 361
 Galactosan, 361
 Galactose, 249, 337, 339*, 343, 345, **346***, 355, 356, 357, 361, 563, 902
 Galactose phenylhydrazone, 326
 Galacto-septanose, 324
 Galacturonic acid, **348***, 361
 Galalith, 168
 Galangin, 557*
 Galegine, 233
 Gallacetophenone, 519
 Gallamine blue, 622
 Gallein, 636
 Gallic acid, 366, **544***, 564, 597, 621, 636
 Gallic acid 4-methyl ether, 552
 Gallic acid trimethyl ether, 841
 Gallobenzophenone, 519
 Gallocatechin, 567*
 Gallocyanine, 622
 Gallotannin, 545
m-Galloyl-gallic acid, 545
 Galloyl-glucose, 546
 Galloylhexoses, 545, 547
 Gas oil, 39, 40
 Gattermann's synthesis, 506, 540
 Gelatin, 308
 Gelatine dynamite, 310
gem, 156, 663
 General effect, 63
 Geneserine, 904
 Geneva nomenclature, **24**, 49, 66, 81, 158, 172, 190
 Genistein, 560
 Genistin, 560
 Gentianose, 356
 Gentiobiose, 351, **353***
 Gentisein, 562
 Gentisin, 562
 Geometrical isomerism, see *Cis trans* isomerism
 Geranic acid, 171, **209**
 Geraniol, **110**, 171, 198, 681
 Germanine, 470
 Germanium alkyls, 148
 Germanium methyl chlorides, 148
 Germanium tetra-*iso*amyl, 148*
 Germanium tetra-ethyl, 148*
 Germanium tetramethyl, 148*
 Germanium tetrapropyl, 148*
 Geronic acids, 709, 710
 Gesarol, 417
 Gesnerin, 563
 Girard's reagent, 296
 Gitogenin, 727
 Gitoxigenin, 725, 726
 Gitoxin, 725
 Glacier blue, 611
 Glaucoobilin, 777
 Gliadins, 304, **307**
 Globin, 772, 776
 Globulins, 304, 305, 307
 Glucoalkaloids, 902
 Glucofuranose, 324

- Glucogallin, 546
 Glucoheptoses, 347
 Gluco-methylose, 345
 Gluconic acid, 325, 330, 343
 Glucononose, 347
 Glucoproteins, 304, 308
 Glucopyranose, 324
 Glucosamine, 308, **348**
 Glucosamine hydrochloride, 349*
 Glucosaminic acid, 348
 Glucose, 89, 329, 337, 339*, 343, **346***, 352, 353, 354, 355, 356, 357, 563, 725, 795, 902, 913, 918
 Glucose, α and β forms, 323*, 339, **346***
 Glucose, open carbonyl form, 324
 Glucose-diethylmercaptal-pentaacetate, 324
 Glucose-diethylmercaptal-pentabenzate, 324
 Glucose-1-phosphate, 90, 351, 359, 360
 Glucose-6-phosphate, 90, 357
 Glucosides, digitalis, 724
 —, interconversion, 301
 6-D-glucosido-D-glucose, 359
 Glucovanillin, 508
 Glucuronic acid, 253, 330, **347**, 350, 561, 703, 717
 Glutaconic aldehyde, 807
 Glutamic acid, 280, 287, 289*, 302, 304, 307, 783, 918
 Glutamine, 288, 289*
 Glutaminic acid, see Glutamic acid
 Glutaric acid, 274*, **280**
 Glutaric acids, alkyl substituted, 659, 700, 704, 709
 Glutaric anhydride, 274
 Glutaric dialdehyde, 853, 863
 Glutathione, 299
 Glutelins, 304, 307
 Glutenin, 307
 Glutin, 304
 Glyceraldehyde, 167, **310**, 334, 342, 344
 Glyceraldehyde phosphates, 90, 91
 Glyceric acid, 303, **311**
 Glyceric acid-di-phosphate, 91
 Glycerides, **213**
 Glycerol, 92, 109, 114, 169, 191, 215, **308***, 811
 Glycerol chlorhydrins, 309
 Glycerophosphates, 218, 310, 360
 Glycerose, 311, 342
 Glyceryl ethers, 310
 Glyceryl nitrates, 310
 Glycine, see Glycocoll
 Glycocholic acid, 293, 716
 Glycocoll, 106, 286, 289*, **295**, 296, 918
 Glycogen, 89, 321, 356, **360***
 Glycol, see Ethylene glycol
 Glycols, 55, **243**, 523, 640, 645, 757
 Glycolaldehyde, 111, **255**, 309, 342, 344
 Glycolaldehyde ether, 256
 Glycolic acid, 252, 257, **261***, 265
 Glycolic ester, 294
 Glycolide, 262
 Glycol nitrate, 246
 Glycolylurea, see Hydantoin
 Glycosidases α and β , 328
 Glycosides, 322, **328**, 346, 563, 599, 638, 727
 Glycylalanine, 297
 Glycylglycine, 297
 Glyoxal, 171, **257**, 318, 378, 389, 459, 655, 794
 Glyoxalic acid, **265**, 306, 317, 459
 Glyoxalines, 257, 793, 795*, 901
 Glyoxal tetramethyl acetal, 774
 Glyoxylic acid, see Glyoxalic acid
 Gnoscopine, 882
 Gold, organic compounds of, **155**, 186
 Gold trimethyl, 155
 Gossypetin, 558
 Gramine, 786
 Graminin, 361
 Grape sugar, see Glucose
 Graphitic acid, 532
 Grignard reagents, see Magnesium alkyl and aryl halides
 Guaiaicol, 365, **435***, 508
 Guaiaicol esters, 435, 508
 Guaiaicol sulphonic acids, 435
 S-Guaiazulene, 745*
 Guanidine, **233**, 829
 Guanines, 233, 826, **829**, 830, 831
 Guanosine, 830, 832
 Guanylic acid, 830, 831, 832, 833
 Gulonic acid, 330
 Gulose, 330, 337, 339*, 341, 343
 Gum arabic, 345
 Gun-cotton, 364
 Gurjunene, 707
 Gutta-percha, 741
 Guvacine, 850*
 Guvacoline, 850
 Gyrophoric acid, 541*
 H-acid, **468**, 489, 493
 Hæm, 772, 773
 Hæmatein, 561
 Hæmatic acid, 773
 Hæmatin, 772, 773
 Hæmatoporphyrin, 773, 775
 Hæmatoxylin, 561
 Hæmin, 771, 773, 775, 777
 Hæmochromogens, 772, 773
 Hæmocyanin, 305
 Hæmoglobin, 305, 772, 773
 Hæmopyrrole, 772*
 Hæmopyrrole carboxylic acid, 782
 Halides, acyl, 220
 —, alkyl, 27, 51, **72**, 82, **157**, 159, 196, **241**
 —, —, halogen exchange, 76
 —, —, nomenclature, 77
 —, —, rearrangement, 76, 391
 —, aryl, **413**, 453, 477, 478
 —, aryl methyl, 401
 —, unsaturated, 77
 Halochromism, 517
 Halogens, quantitative estimation of, 8
 ω -Halogen acyl acetic esters, 749
 Halogen carriers, 387, 413
 Halogen substituted acids, 138, 205, **253**, 264, 265, 285, 533
 — — aldehydes, 791
 — — ketones, 790, 791, 792
 Halogeno salts, 387
 Harden-Young ester, 90
 Harmalane, 898
 Harmaline, 898*
 Harman, 898*
 Harmine, 897, 898*
 Hashish, 552, 553
 Heavy hydrogen, see Deuterium
 Heavy nitrogen, 918
 Heavy oil, 383
 Heavy oxygen compounds, 917
 Hederagenin, 727
 Hedonal, 231
 Helianthine, 488
 Helicin, 104, **507**
 Helindon yellow C.M., 586

- Helminthosporin, 599
 Hemiacetals, cyclic, 256, 323, 339
 Hemicellulose, 367
 Hemimellitene, 392*, **393**, 531
 Hemimellitenols, 433
 Hemimellitic acid, 531*, 898
 Hemipinic acid, 876, 881, 885, 887
 Hemlock alkaloids, 846
 Heneicosane, 30*
 Hentriacontane, 30*, 36
 Heptacene, 413
 Heptacontane, 29, 30*, 37
 Heptacosane, 36
 Heptadecane, 30*
 Heptadecyl cyanide, 188*
 Heptane, 23, 30*, 35, 40, 52
 Heptene, 52*, 54
 Heptyl alcohols, 85*, 88, 169
 Heptyl cyanide, 188*
 Heptyl mercaptan, 119*
 Heptitols, 314
 Heptoic acid, see Oenanthalic acid
 Heptoic aldehyde, see Oenanthal
 Heptoses, 347
 Heptylamine, 131*
 Heptylene, see Heptene
 Heptylic acid, see Heptoic acid
 Heptyne, 169
 Heptyne carboxylic acid, 169, 210
 Hercynine, 796
 Herniarin, 551
 Hesperetin, 559
 Hesperidin, 559
 Hesperitic acid, 543*, 559
 Heteroauxin, 786
 Heterocyclic compounds, 755
 —, nomenclature, 755
 Heterocyclic rings, five-membered, 755, 757
 —, six-membered, 756
 Heteroxanthine, 828
 Hexabromobenzene, 394
 Hexacene, 413
 Hexachlorobenzene, 417*
 Hexachlorocyclohexanes, 387*
 Hexachloroethane, 72, 252*
 Hexacontane, 30*
 Hexadecane, 30*
 Hexadecene (= hexadecylene), 52*
 Hexahydrocinnamic carboxylic acids, 408
 Hexahydromellitic acid, 532
 Hexahydrophenylalanine, 303
 Hexahydrophenylene-diacetic acids, 408
 Hexahydrophthalic acids, 660, **692***, 747
 Hexahydrophthalic acid anhydrides, 692*, 742
 Hexahydroxybenzene, 442, 655, 676
 Hexaiodobenzene, 394
 Hexamethylbenzene, 381, **394***, 532
 Hexamethyldiamino-biphenyl, 396
 Hexamethyldisilane, 146*
 Hexamethyldisiloxane, 147
 Hexamethylene glycol, 247*
 Hexamethylenediamine, 281
 Hexamethylene-tetramine, 167, 835
 Hexamethylethane, 146*
 C-Hexamethyl-phloroglucinol 440
 Hexamylose, 359
 Hexane, 23, 30*, 35, 389, 642
 Hexanitro-biphenyl dicarboxylic acid, 396
 Hexanitrodiphenylamine, 465
 Hexaphenylethane, 400
 Hexenaldehyde, 682
 Hexene, 52*, 383
 Hexitols, **314**, 333, 339*
 Hexogen, 168
 Hexokinase, 91
 Hexonic acids, 333
 Hexoses, 321, 331, **337**, **346**, 759
 Hexyl alcohols, 85*, 88, **108**
 Hexyl bromide, 74*
 Hexyl butyrate, 211*
 Hexyl chloride, 74*
 Hexyl cyanide, 188*
 Hexyl iodide, 74*
 Hexyl mercaptan, 119*
 Hexylamine, 131*
 Hexylene, see Hexene
 Hippuric acid, 293, 521, 786
 Histamine, 291, 795*, 905
 Histidine, 287, 288, 289*, 291, 306, 795, 918
 Histones, 304, 307
 History of organic chemistry, 17, 943
 Hoesch-Houben ketone synthesis, 510
 Hofmann's degradation of amides, **130**, 250, 453
 — quarternary ammonium compounds, **133**
 See also Exhaustivemethylation
 Homarine, 811
 Homatropine, 857
 Homoapocamphoric acid, **640**, 703
 β -Homochelidonine, 896
 Homocincholoipone, 872
 Homolka's Base, 606
 Homologous compounds, 23
 Homomeroquinene, 873
 Homopilopic acid, 901
 Homoterpenyl methyl ketone, 679
 Homoterpenylic acid, 680
 Homoveratric acid chloride, 876, 877
 Homoveratrole, 876
 Homoveratroyl chloride, 877
 Homoveratrylamine, 877
 Honeystone, 532
 Hordein, 307
 Hordenine, 291, 841*, 874, 905
 Hormones, 38, 462, 539, **717**, 724
 Horn, artificial, 168
 Hycar, 741
 Hydantoic acid, 296
 Hydantoins, 276, **296**, 796, 833
 Hydnocarpic acid, 658
 Hydraldite, 168
 Hydramine fission, 839, 868, 870, 882
 Hydrastic acid, 884, 885
 Hydrastine, **883***, 908
 Hydrastinic acid, 884
 Hydrastinine, 883, 886
 Hydratropic acid, 525
 Hydrazides, 195, **226**, 523
 Hydrazidines, 226
 Hydrazine, 294, 796, 798, 817
 Hydrazines, acyl, 802
 —, alkyl, **136**, 294, 796, 798
 —, aryl, **480**, **497**, 796, 798
 Hydrazobenzene, 497*
 Hydrazo-compounds, 136, 451, **497**
 Hydrazodicarboxylic acid, 263
 Hydrazones, see also Phenylhydrazones, 130, 162, 249
 Hydrazonium salts, 136
 Hydrindene, 404
 Hydro-acridines, 631
 Hydroaromatic compounds, 384
 Hydrobenzamide, 505
 Hydroberberines, 886
 Hydrocarbons, aliphatic, **22**, 383, 913
 —, —, unsaturated, 43
 See also Ethylenes

- Hydrocarbons, aromatic, 39, **383**, 425, 478, 524, 744, 913
 —, —, unsaturated, 402
 Hydrocellulose, **365**, 367
 Hydrocinchonidine, 869*
 Hydrocinchonine, 865, **869***
 Hydrocotarnine, 879
 Hydrocotoin, 518*
 Hydrocoumaric acids, 538*
 Hydrocupreine, 874
 Hydrocupreine ethers, 873
 Hydrocyanic acid, 160, **184**, 185*, 273, 803
 See also Hydrogen cyanide
 Hydrocyanocarbodiphenyl-imide, 571
 Hydrogen, detection of, 3
 —, estimation of, 5, 10
 —, heavy see Deuterium
 Hydrogen acceptor, 86
 Hydrogen atom, mobile, 140, 482
 Hydrogen bond, 127, 520
 Hydrogen carrying co-ferment, 731
 Hydrogen chloride type, 20
 Hydrogen cyanide, 70, 160, 383
 See also Hydrocyanic acid
 Hydrogen type, 20
 Hydrogenation, 215, 641, 660, 674
 —, heat of, 380
 Hydrohydrastinine, 884
 Hydrojuglone, 587
 Hydron blue, 629
 Hydronaphthalene, 407
 Hydroperoxides, 55
 Hydroquinidine, 865, **874***
 Hydroquinine, 865, **874***
 Hydroquinolines, 812, 813
 Hydroquinone, **438***, 439, 576, 594, 661, 913
 Hydroscopoline, 858
 Hydouracil, 798
 Hydroxamic acids, 166, 195, **225**, 523
 Hydroxamic acids, 226, 524
 Hydroxyacetophenones, **517***, 554, 555, 565
 Hydroxyacids, see Hydroxycarboxylic acids
 Hydroxyaldehydes, 164, **255**, 321
 Hydroxyaminobutyric acid, 900
 Hydroxyaminopropane, 901
 Hydroxyamylquinoline, 812
 —, methyl ether, 812
 Hydroxyanthracenes, 443*
 Hydroxyanthraquinones, 410, **592**
 Hydroxyazobenzenes, 482, 496
 Hydroxybenzalacetophenone, 555
 Hydroxybenzaldehydes, 444, 506
 Hydroxybenzoic acids, 374, **535**, **537***, 539, 563
 Hydroxybenzylisothiocyanate, 241
 Hydroxyberberine, 884
 Hydroxybutyric acid, 197, **263***
 Hydroxycamphors, 703
 Hydroxycarboxylic acids, aliphatic, 205, 206, 254, **261**, 315, 333–343, 641
 —, aromatic, 535, 548
 —, stereochemistry, 102, 302, 333–343
 Hydroxychlorostyrene, 761
 Hydroxycholanolic acids, 717
 Hydroxycinnamic acid, **538**, 560, 563
 Hydroxycoumaranones, 762
 Hydroxyethylamine, see Colamine
 Hydroxyethyl hydrogen peroxide, 118
 Hydroxyethylmethylamine, 869
 Hydroxyflavones, 556
 Hydroxyflavonols, 556
 Hydroxyfumaric acid, 316
 Hydroxyglutamic acid, 287, 289*
 Hydroxyhexadecenoic acid, 265
 Hydroxyhydrastinine, 884
 Hydroxyhydroquinone, 439*
 Hydroxyketones, **255**, 321, 505
 —, phenolic, 511, 517, 520
 Hydroxyketones, from corpus luteum, 720*
 Hydroxylactone forms, 265
 Hydroxylaevalinic aldehyde, 271
 Hydroxylamine, 238
 Hydroxylamines, **137**, **422**, 452
 Hydroxymaleic acid, 316
 Hydroxymaleic anhydride, 316
 Hydroxymenthylic acid, 668
 Hydroxymethoxynaphthalene carboxylic acid, ethyl ester, 644
 Hydroxymethoxytoluene quinone, 568
 Hydroxymethylene-cyclohexan-2-one, 813
 ω -Hydroxy-methyl-furfural, 271, 330, 759*
 Hydroxynaphthoic acid anilide, 495
 α -Hydroxynitriles, 161, 188
 See also Cyanhydrins
 15-Hydroxypentadecanoic acid lactone, 264*
 Hydroxyphenanthrenes, 889, 890, 893
p-Hydroxyphenylacetone nitrile, 840
p-Hydroxyphenylalanine, see Tyrosine
p-Hydroxyphenylarsonic acid, 501
o-Hydroxyphenylethanol, 762
p-Hydroxyphenylethylamine, 291, 840*
p-Hydroxyphenyllactic acid, 291
 4-Hydroxyphenylpiperidinium salts, 135
 Hydroxyproline, 287, 289*, 303, 768, 783*, 787, 842
 Hydroxypropionic acids, 262, 263
 Hydroxypurines, 823, 827, 828
 Hydroxypyrrromethanes, 776
 Hydroxyquinolines, 473, 814
 7-Hydroxyisoquinoline, 873
 Hydroxyquinoline carboxylic acid, 786, 815
 Hydroxyresveratrol, 444
 Hydroxystearic acid, 216
 Hydroxysulphonic acids, 161
 Hydroxythionaphthen, 575, 767*
 Hydroxythionaphthen carboxylic acid, 767
 Hydroxytryptophane, 787
 Hydroxyvaline, 901
 Hygrine, 842*, 859, 906
 Hygrinic acid, 303, 783, 843, 844
 Hygroline, 843
 Hyoscyamine, 857, 858*
 Hypaphorine, 787
 Hypnone, 514
 Hypochlorous esters, 112
 Hypothiocyanic acid, 273
 Hypoxanthine, 826, **828**, 830
 Hypoxanthosine, 830
 Hypsochromic group, 485
 Hyraldite, 572
 Hystazarin, 594, 596

- Ice colours, 495
 Idæin, 563
 Iditol, 314*, 339
 Idosaccharic acid, **339**, 676
 Idose, 337, 339*, 341
 Igelite, 79
 Imidazoles, 257, 259, 756, 793
 Imidazole homologues, 794
 Imidazole magnesium bromide, 794
 Imidazole potassium, 794
 Imidazolone, 298
 β -Imidazolylalanine, see Histidine
 Imidazylethylamine, 291
 Imide-sulphuric acid, 188
 Imido-ethers (or -esters), **188**, 220, 224, 273, 523
 Imido-halides, 188, 242
 Imido-acids, 292
 Imino-carbonic acids, 236
 Iminocarboxylic acids, 286
 Imino-nitriles, 749
 Iminophthalimide, 788
 Immedial black, 628
 Immedial indones, 628
 Immedial pure blue, 627
 Immedial yellow, 630
 Imonium salts, 583, 606
 Imperatorin, 763
 Indamines, **584**, 616
 Indamine blue, 621
 Indanthrene blue, 601
 Indanthrene bordeaux B, 603
 Indanthrene brilliant green B, 603
 Indanthrene dark blue BO, 603
 Indanthrene golden orange G, 602
 Indanthrene golden yellow G.K., 602
 Indanthrene red BN, 605
 Indanthrene violet R extra, 603
 Indanthrene violet RN, 605
 Indanthrene yellow G, 601
 Indanthrene yellow 3 G.F., 604
 Indene, 384, **404***, 653
 Indican, 567, 568, 768, 783
 Indicators, pH, 610, 940
 —, radioactive, 911
 Indigo, 1, **567**, 571*
 Indigo brown, 568
 Indigo disulphonic acid, 572
 Indigo dyeing, 572
 Indigo gluten, 568
 Indigo, halogenated, 573
 Indigoids, 571, **573**, 574
 Indigo MLB 5B, 573
 Indigo red, 568, **574**
 Indogenides, 574
 Indigosols, 573
 Indigo synthesis, 569
 Indigo white, 572
 Indigotin, see Indigo
 Indirubin, see Indigo red
 Indogenides, 574
 Indole, 568, 569, 755, **783**, 786*, 918
 Indole homologues, 784
 Indole-3-acetic acid, or Indolylacetic acid, 786
 β -Indole aldehyde, 785, 786
 Indole-lactic acid, 282
 "Indolenine formula", 783, 785
 β -Indolyl-propionic acid, 786
 Indophenin reaction, 385
 Indophenols, **583**, 627
 Indophenol blue, 584
 Indoxyl, 567, **568***, 570, 784
 Indoxyl-glucuronic acid, 347
 Indoxylic acid, 571
 Indoxylsulphuric acid, 292, 568
 Induced effect, 63
 Indulines, 620
 Indyl-magnesium salts, 785
 Ink, 544
 Inosine, 830, 832
 Inosinic acid, 830, 832
 Inositols, 101, 662, **664**, 675*, 677
 Inosose, 676
 Insulin, 724
 Inulases, 360
 Inulin, 356, **360***
 Invertase, 353
 Invert sugar, 353
 Iodides, acyl, 195, **220**
 —, alkyl, 116
 Iodine, tervalent compounds, 416
 Iodine green, 614
 Iodival, 232
 Iodoaclys, 196
 Iodobehenic acid, 255
 Iodobenzenes, **414***, 415, 477
 Iodobenzoic acids, 533
 Iodochlorides, 416
 Iodocyclopentane, 643
 Iodoform, 88, 157, 177, **184***
 Iodogorgoic acid, **287**, 539
 Iodol, 771
 Iodomethyl-trimethyl-ammonium iodide, 134
 Iodonium compounds, 416
p-Iodophenol, 445*
 4-Iodoresorcinol dimethyl ether, 389
 Iodosobenzene, 415
 Iodostarin, 255
 Iodoxybenzene, 416
 Ion-bond, 63
 Ionones, 179, 687*
 —, bromophenyl hydrazones, 688*
 —, semicarbazones, 688*
 Irene, 688
 Iricyanogen, 835*
 Irigenin, 560
 Irisin, 361
 Irone, 688*
 Isatin, 385, **568**, 569, 575, 644, 784, 815
 Isatin- α -anilide, 571, 575
 Isatin chloride, 575, 784
 Isatinic acid, 815
 Isatogenic acid, 569
 Isethionic acid, 247
 Iso-forms, 139
 Isomerase, 91
 Isomerides (number of), alcohols, 928
 —, aliphatic compounds, 928
 —, cyclic hydrocarbons, 929
 —, paraffins, 24, 928
 —, substitution products, 929
 Isomerism, 18, 21, 24, 77, 381, 406
 Isomerism, chain, 24
 —, dynamic, 642
 Isoprene, **61***, 157, 579, 671, 705, 740, 741
 Isotopic elements, **911**
 Isoxazole, 756
 Itaconic acid, 284*
 Janus red, 487
 Jasmone, 655
 Juglone, 586*
 Julin's carbonchloride, 417
 Kampferide, 557
 Kampferol, 557*
 Kephalin, **219**
 Keracyanin, 563
 Kerasine, **249**
 Keratins, 304, 308
 Kermes (kermisic acid), 598
 Kerosene, 39, 40, 41
 Ketene, **179**, 222, 646
 Ketenes, **180**, 606
 Ketene acetal, 278
 Ketene oxides, 181

- Ketimides (= Ketimines),
 176, 511, 762
 Keto-aldehydes, 791, 796
 Ketocamphor, 703
 Keto-carboxylic acids, **266**,
 285, 286, 641
 —, α , 292, 459, 800, 917
 —, β , 197, **267**, 554, 749, 796,
 798
 —, β , esters, 808, 818
 —, γ , 271
 —, δ , 264
 Keto-enol tautomerism, 109,
 267, 440, 444, 516, 536, 568,
 821, 823
 Keto (= carbonyl) form, 109,
 268
 5-Ketogluconic acid, 760
 α -Ketoglutaric acid, 320
 Ketohexoses, 321, 322, 344
 Ketols, 256
 Ketones, aliphatic, 55, 82, 117,
 172, 244, 653, 809, 812
 —, aromatic, 503, **509**, 516,
 653
 —, aromatic-aliphatic, 392,
 509, 516
 —, cyclic, 640, 641, 644, 654,
 682, 749
 —, esocyclic-exocyclic, 650
 —, nomenclature, 172
 —, unsaturated, 796
 Ketone-acetals, 175
 Ketone-amines, 176
 Ketonic hydrolysis, **270**, 317
 Ketonimides, 173
 Keto-nitriles, 749
 Ketoses, 321, 329, 332, 338,
 343, 344, 676, 759
 Ketoximes, **176**, **512**, 641
 —, stereochemistry of, 511
 Ketyls, metallic, 175
 Kluyver's inosose, 676
 Kojic acid, 806
 Kolbe synthesis, 29, 67, 535
 Koproglaucobilin ester, 778
 Koprohaemin, 778
 Koproporphyrin, 774
 Kryptopyrrole, 772*, 774
 Kryptopyrrole carboxylic acid,
 782
 K-strophanthoside, 726
 Kynurenic acid, 786, 787, 815
 Kynurenine, 787

 Labelled atoms, 911
 Lactalbunin, 305, 307
 Lactams, 299, 870
 Lactases, 355
 Lactic acid, 1, 13, 258, **262***,
 304, 355, 360, 838
 —, salts, 263
 Lactic acid fermentation, 262,
 360
 Lactic anhydride, 263
 Lactide, 263
 Lactobioses, 351
 Lactoflavin, 730
 Lactoglobulin, 305, 307
 Lactones, **263**, 332, 682
 Lactose, 354*
 Lævoglucosan, 342
 Lævopimaric acid, 708
 Lævulinic acid, **170**, 202, **271**,
 655, 706, 766
 Lævulinic aldehyde, 171
 Lakes, 486, 491, 519, 595, 622,
 636
 Laminarin, 361
 Lanthionines, 286, 289*
 Lapachol, 588*
 Laudanidine, 878
 Laudanine, 878
 Laudanosine, **877***, 908
 Lauric acid, 33, 193*, 203, 217
 Lauric aldehyde, 169
 Lauryl chloride, 221*
 Lauth's violet, 461, **624**
 Lawsons, 588
 Lead, organic compounds of,
 150
 —, sugar of, 201
 Lead alkyl salts and bases, 150
 Lead diphenyl, 151
 Lead ditcyl, 151
 Lead tetraacetate, 246
 Lead tetra-alkyls, 150
 Lead tetraethyl, 150
 Lead tetramethyl, 150
 Lead trialkyl hydroxides, 150
 Lead tricyclohexyl, 150
 Lecanoric acid, 312, **541***
 Lecithins, 218
 Legumelin, 305, 307
 Lentin, 460
 Lepidine, 814*, 815
 Leptazole, 804
 Leucines, 97, 287, 288, 289*,
 302
 Leucinol, 290
 Leuco-base, 606
 Leuco-compound, 572
 Leuconic acid, 655
 Leucopterin, 833
 Leucosin, 307
l-Leucyltriglycyl-*l*-leucyltri-
 glycyl-*l*-leucyloctaglycyl-
 leucine, 298
 L-forms, series, 105
l (= lævo) forms, 99
 Lichenin, 366
 Lichen substances, 540
 Liebermann's reaction, 430,
 432
 Light oil, 383
 Lignin, **365**, 441
 Lignoceric acid, 33, 203, 249
 Limettin, 552*
 Limonenes, 662, 666, 668,
 670*, 680
 Limonene bromides, 670, 672*
 Linalool, **110**, 669
 Linoleic acid, **209***, 215, 218
 Linolenic acid, 210
 Lipases, 215, 858
 Lipochromes, 556, **708**, 778
 Lithium, organic compounds
 of, 156, 749
 Lithium alkyls, 28, **156**, 173
 Lithium aryls, 156, **503**
 Lithium butyl, 156, 503
 Lithium phenyl, 389, 503
 Lithium picolyl, 864
 Lithocholic acid, 716, 717
 Litmus, 438
 Lobelanine, 853, 856
 Lobeline, 852
 Loiponic acid, 866, 869
 Lomatiol, 588
 Lossen's rearrangement, 226
 Lubricating oil, 39, 40
 Lumi-auxone a, 659
 Lumichrome, 731
 Lumiflavin, 731
 Luminal, 279
 Lumisterol, 735
 β -Lupinane, 865
 Lupinic acid, 864
 Lupinine, 864*
 Luteolin, 557*
 Lutidines, 809*
 Lutidinic acid, 811*
 Lycopene, 708
 Lyochromes, 730
 Lysergic acid, 910
 Lysine, 251, 287, 288, 289*,
 291, 302, 907, 918
 Lysol, 433
 Lyxose, **334**, 336, 341, **343**,
 349

 "M. and B. 693", 808
 Maclurin, 519*
 Magdala red, 620
 Magnesium alkyl salts, 29, 75,
 83, 141, 144, 145, 148–150,
 152–5, 159, 191, 643, 770

- Magnesium aryl salts, 415, 523, 643, 894
 Magnesium, organic compounds of, 151
 Malachite green, 610
 Malamide acid, 303
 Maleic acid, 68, **281**, 283*, 390, 580, 654, 758
 Maleic acid dinitrile, 283
 Maleic anhydride, 60, **282**, 316, 654
 Maleic dialdehyde, 817
 Maleic imide, 773
 Maleinoid form, 282
 Malic acids, 1, 254, 277, 280, 281, 300, 303, 304, **315***, 320, 550, 820, 838, 917
 Malonic acid, 181, 274*, **277**, 913, 914*
 Malonic acid, C alkyl derivatives, **277**, 709
 Malonic ester synthesis, 205, 639, 692, 745
 Malonyl chloride, 278
 Malonyl urea, see Barbituric acid
 Maltase, 94, 353
 Maltobionic acid, 358
 Maltol, 806*
 Maltoses, 93, **353***, 354, 358, 360
 Malt-sugar, see Maltose
 Malvin, 564
 Mandelic acid, 548*, 916
 Mannans, 346, 356, 362, 365, 367
 Manninotriose, 356
 Mannitol, 114, **314***, 332, 339, 343, 913
 Mannobiose, 367
 Manno-ketoheptose, 347*
 Mannonic acid, 330, 343
 Mannononose, 347
 Mannosaccharic acid, 339*
 Mannose, 329, 330, **337**, 339*, 341, 343, **346**
 Mannose-phosphate, 90
 Mannuronic acid, 348*
 Mannuronolactone, 348*
 Margaric acid, 193*
 Markovnikov's rule, 54
 Marsh gas, 33
 Martius' yellow, 449
 Matricaria camphor, 699
 Mauveine, 617, 619
 Mecocyanin, 563
 Meconic acid, 806, 838
 Meconin, 879, 882
 Meerwein-Ponndorf reduction, 160
 Melamine, 237, 835
 Meldola blue, 622
 Melezitose, 356
 Melene, 58*
 Melibiase, 355
 Melibiose, 355*
 Melilotic acid, 538*
 Melissic acid, 203
 Melissyl alcohol, 108
 Mellitic acid, 394, **531***
 Mellophanic acid, 531*
 Menthadienes, 668
m-Menthane, **666**, 672
p-Menthane, 662, **665**, 693
 Menthenes, 666, 667*, 669
 Menthenol, 673
 Menthanonones, 669, 684*
 Menthols, 347, 667, **678***, 679*, 684
 Menthones, 683*
 Mepacrine, 633
 Mercaptals, 162
 Mercaptans, 39, 113, **119**, 153, 162, 175
 Mercaptides, **120**, 240
 Mercaptols, 175
 Mercerization, 365
 Mercury cyanide, 185
 Mercury diethyl, 155*
 Mercury dimethyl, 155*
 Mercury diphenyl, 500
 Mercury dipropyl, 155*
 Mercury fulminate, 238
 Mercury, organic compounds, of, 151, **155**
 Mercury succinimide, 280
 Meroquinene, 866, 870
 Mesaconic acid, 284*
 Mesidine, 458
 Mesitol, 429, 433
 Mesitylene, 176, 390, 392*, **393**, 483, 531
 Mesitylene sulphonic acid, 429
 Mesityl oxide, 176, 178
Meso-form, 107
Meso(*ms*)-position, 410, 468
 Mesobilirubin, 777
 Mesobilirubinogen, 777
 Mesohæmin, 778
 Mesomerism, **66**, 127, 379, 608, 797, 805, 807
 Mesoporphyrin, 773, 779
 Mesoxalic acid, **317***, 656
Meta-, 382
 Metachloral, 253
 Metafulminuric acid, 239
 Metahemipinic acid, 887, 897
 Metaldehyde ('meta'), 169
 Metamerism, 125
 Metanil yellow, 488
 Metanilic acid, **466**, 488
 Metastyrene, 403
 Methæmoglobin, 772, 773
 Methane, 23, 26, 27, 30*, **33**, 126, 383
 Methane-d₄, 912
 Methane fermentation, 26, 33
 Methane type, 21
 Methanol, see Methyl alcohol
 Methionine, 248, 287, 288, 289*, 293, 302
 Methoxyacetophenone, 432
 Methoxybenzophenone oximes, 513*
 Methoxyphthalic acids, 892
 Methoxyquinoline, 815, 870
 Methoxyquinonyl-alkylketones, 869
 Methoxysuccinic acid, 303
 Methyl, 150
 Methyl acetate, 87
 Methyl alcohol, 17, 81, 84, 85*, **87**, 199
 Methyl amyl ketone, **178**, 217
 Methyl anthranilate, 87, **534***
 Methylacetanilide, 469*
 Methylacetoacetic acid, 258
 —, ester, 258, 271
 Methylacetylene, 67, 77, 390
 Methyl-allyl-tetrahydroquinolinium salts, 135
 Methylamine, 131*, 133, 855, 860, 863
 Methylaminoethyl alcohol, 248, 890
 Methyl-aminonaphthalene, 898
 Methylanabazine, 843
 Methylaniline, 455*
 Methylanthranil, 569
 Methylanthranilic acid, 899
 —, methyl ester, 534*
 Methylarbutin, 438
 Methylarsine, 144*
 Methylarsonic acid, 144
 Methylarsonium iodide, 144
 Methyl benzoate, 522*
 Methyl benzyl ether, 503
 Methyl bromide, 74*
 Methyl butyl ketone, 217
 Methyl chloride, 17, 32, 74*, **76**, 849
 Methyl chlorocarbonate, 229*
 Methyl cyanides, 188*, 189
 Methyl ethyl ketone, 173, 258
 Methyl fluoride, 77*
 Methyl formate, 14, 16
 Methyl green, 614

- Methyl heptyl ketone, 178, 217
 Methyl hexyl ketone, **217**, 706
 Methyl hypochlorite, 112*
 Methyl iodide, 74*, **76**
 Methyl iodochloride, 416
 Methyl mercaptan, 119*
 Methyl nitrite, 138*
 Methyl nonyl ketone, 178, 217
 Methyl octyl ketone, 178
 Methyl orange, 488
 Methyl orthoformate, 220*
 Methyl phosphate, 114*
 Methyl isopropyl ketone, 59
 Methyl salicylate, 87, 535, 537*
 Methyl sulphite, 113*
 Methyl isothiocyanate, 241*
 Methyl undecyl ketone, **178**, 217
 Methyl violet, 613
 Methyl-butyl-ethoxyoxazole, 790
 Methylcolamines, 248, 888, 889
 Methylconiine, 847*, 907
 Methylcyanoacetyl urea, 820
 Methylcyclohexane, 642, **665***, 742
 Methylcyclohexanone, 106, 706
 Methylcyclohexene, 666*
 Methyl-cyclohexylidene-acetic acid 101, 690*
 Methylcyclopentane, 389, 642
 Methylcyclopentenophenanthrene, 714, 725, 727
 Methylcyclopropane, 641, 645*
 Methylcymene, 661, 674
 Methylcytosine, **819**, 830
 Methyl-diethyl-methane, 15
 Methyldihydroxypyrimidine, 270
 Methyl dodecyl aldehyde, 169
 Methylene, 49, **57**
 Methylene blue, 624
 Methylene bromide, 158*
 Methylene chloride, 32, 100, **158***
 Methylene green, 625
 Methylene iodide, 158*
 Methylene violet, **626**, 627
 Methylenecyclobutane, 644
 Methylenecyclohexane, 666*
 Methylene-dioxyhydrindone, 880
 Methylenurea, 232
 Methylephedrine, 839
 Methyl-ethyl-acetic acid, 202*
 Methyl-ethyl-benzenes, 393*
 Methyl-ethyl-propyl-isobutyl-ammonium chloride, 134
 Methyl-ethyl-propyl-tin iodide, 149*
 (9-Methyl-9-fluorenyl) trimethylammonium iodide, 134
 Methylfuran, 758*
 α -Methylgalactoside, 342
 Methylgentiobioside, 352
 N-Methylglucosamine, 677
 Methylglucosides, 327, 342
 Methylglyoxal, 90, **257**, 378, 908
 Methylglyoxalines, 901
 Methylgranatanine, 746
 N-Methylgranatenine, 746
 Methylgranatic acid, 863
 N Methylgranatolines, 746, 863
 N-Methylgranatonine, see Pseudopelletierine
 Methylheptanone, 714
 Methylheptenone, 110, 171, **179***, 708
 Methylhexahydrolutidinic acid, 858
 Methylhexanes, 35*
 Methylhydrocotoin, 518*
 Methylhydroxamic acid, 166
 Methyl-hydroxyethyl-thiazole 729
 Methylhydroxylamines, 137*
 N-Methyl-hydroxypiperidine-carboxylic acid, 850
 Methylimidazoles, 330, 795
 Methylindene, 404
 Methylindoles, 783, 785, 786*
 Methyl-isoxazolone, 270
 Methylmannoside, 342
 Methylmenthatriene, 661, **674**
 Methyl-methoxypyridine-dicarboxylic acid, 732, 733
 Methyl-methoxy-pyridone, 851
 α -Methylmorphimethine, 888, 889
 Methyl-naphthaquinone, 737
 Methylnicotinic acid, 849
 Methylnicotone, 844
 Methylnipecotinic acid, 850
 Methylnitranilide, 472*
 Methyl-nonyl aldehyde, 169
 Methyl-norcamphor, 704
 Methyl-nor-homocamphoric acid, 704
 Methylolurea, 232
 Methylpalmitic acid, 204
 Methylisopelletierine, 864
 Methylpentanes, 25, 31
 Methylpentanol, 108
 Methylpentoses, 322, 345, 678
 Methyl-phenyl-methylamine, 914*
 Methyl-phenyl-methylamine-d₂, 914*
 Methylphenyloxazole, 790
 Methylphenylthiazole, 791
 Methylphosphine, 142*
 Methylpiperonal, 896
 Methylpyrazoles, 797
 Methylpyridone, 808
 Methylpyrrolidine, 242, 843
 Methylpyrrolidine carboxylic acid, 843
 Methylpyrrolidone, 845
 Methylpyrroline, 843, 851
 Methylquinolines, 812, 813*, 814*
 Methylsilicone polymers, 148
 Methylstearic acid, 204
 Methylsuccinic acid, 766
 N-Methylsuccinimide, 854
 Methyltetronic acid, 761
 Methylthebaol, 890
 Methylthiophens, 766*
 Methyl-triaceton-alkamine, 857
 Methyltropidines, 743
 Methylxanthines, 827, 828
 Metol, 469
 Mezcaline, 841
 Miazine, 756, 817
 Michler's ketone, **456**, 613
 Micro-elementary analysis, 8
 Middle oil, 383
 Migration, acyl, 87, 214, 511, 769
 —, alkyl, 269, 769, 794
 Milk sugar, see Lactose
 Millon's reaction, 306
 Mineral oil, 26, 37, 637, 652, 662
 —, world production, 931
 Mineral wax, 26, 41
 Molecular formulæ, 12
 Monardaecin, 563
 Monocrotaline, **846**
 Monosaccharides, 321
 See also Sugars
 Monotropitoside, 535
 Mordant dyes, 486, **491**, 519, 556, 560, 582, 595
 Mordants, 199, 201, **486**
 Morin, 519, **558***,
 Morphenol, 764*, 890

- Morphenol, methyl ether, 889
 Morphines, 104, 248, **888**, 891, 892*
 Morphol, 764, 889, 890
 Morphol methyl ethers, 889
 Morphothebaine, 894
 Mucic acids, 1, **338**, 339*, 675, 760, 768
 —, β -aminopyridine compound, 844
 Mucins, 304, 308
 Mucoids, 308
 Muco-inositol, 664, 677
 Muconic acids, 390*
 Murexide reaction, 825
 Muscarufin, 581
 Muscle-adenylic acid, 830, 832
 Muscone, 751
 Musk, artificial, 421
 —, natural, 733
 Mustard gas, 244
 Mustard oil test, 132
 Mustard oils, see *iso*Thiocyanic esters
 Mutarotation, 323, 326
 Mutase, 200
 Mutatoxanthin, 711
 Myogen, 307
 Myosin, 307
 Myrcene, 61, 707
 Myricetin, 558*
 Myricyl alcohol, 108
 Myricyl bromide, 74*
 Myricyl cerotate, 213
 Myricyl chloride, 74*
 Myricyl iodide, 74*
 Myricyl palmitate, 213
 Myristic acid, 33, 193*, 203, 217
 Myristicin, 439*
 Myristicin aldehyde, 881
 Myristone, 174*
 Myristyl chloride, 221*
 Myrtenal, 698
 Myrtenol, 698

 Naphtha, solvent, 384
 Naphthacene, 412
 Naphthalene, 383, 384, **405**, 407*, 529, 571
 Naphthalene substitution, isomerism, 406
 Naphthalenedisulphonic acids **425**, 496
 Naphthalene-indolindigo, 575
 β -Naphthalenesulphonic acids **424**, 442, 548
 Naphthalenetrisulphonic acids 425
 Naphthalic acid, 531*
 —, anhydride, 531*
 Naphthaquinones, 407, 587*
 Naphthaquinone derivatives, 736
 Naphthaquinone dyes, 587
 Naphthaquinone oximes, 589
 Naphthazarin, 588
 Naphthazine, 616
 Naphthenes, 39, 43, **637**, 662
 Naphthenic acids, 39, **656**
 Naphthionic acid, **467**, 488, 493
 α -Naphthol, 406, **442***, 461, 483, 488
 β -Naphthol, 430, **442***, 461, 483, 487, 495, 575, 630
 Naphthol AS, 495
 α -Naphthol blue, 584
 Naphthol blue-black B, 489
 Naphthol green, 589
 Naphthol orange, α and β , 488
 Naphthol yellow, 449
 Naphtholdisulphonic acids, **446**, **447**
 Naphtholsulphonic acids, **446**, 447
 1-Naphthol-4-sulphonic acid, **446**, 447, 494
 2-Naphthol-8-sulphonic acid, **446**, 447, 489
 Naphtholtrisulphonic acids, 446, 447
 Naphthophenazine, 616
 α -Naphthylamine, 405, 428, 442, **461***, 483, 495, 620
 β -Naphthylamine, 428, 430, 442, **461***, 483
 Naphthylamine black D, 489
 Naphthylamine Bordeaux, 495
 Naphthylamine disulphonic acids, 428, **467**
 Naphthylamine sulphonic acids, 428, **466**, 467
 Naphthylamine trisulphonic acids, 467
 Naphthylenediamine, 483
 Naphthylenediamine disulphonic acid, 493, 494
 Narceine, **882***
 Narcotine, **878**, 882*,
 Narcylene, 72
 Naringenin, 559
 Natural gas, 26, 38
 Negative substituents, 140, 415
 Neobilirubic acids, 776
 Neocid, 417
 Neolan dyes, 492
 Neo-nerolin, 443*
 Neosalvarsan, 502
 Neostibosan, 503
 Neoxanthobilirubinic acids, 777
 Neradols, 168, 548
 Nerol, **110**, 171, 681
 Nerolidol, 705
 Nerolin, 443*
 Nervonic acid, 209*
 Neuberg ester, 90
 Neurine, 248
 Neutral red, 616
 Neutral violet, 617
 Neville-Winther's acid, 447
 New blue R, 622
 Ngai-camphor, 700
 Nicotinamide, 731, 733
 Nicotine 101, 303, 768, 838, 843*, 907
 Nicotinic acids, 811*, 844, 849
 Nicotinic ester, 845
 Nicotone, 303
 Nicotyrine, 844
 Nigraniline, 585
 Nikethamide, 811
 Ninhydrin, 516
 Ninhydrin reaction, 306, 516
 Niobe oil, 522
 Nirvanol, 296
 Nitramines, 464
 Nitranilides, **471***, 480
 o -Nitraniline, 458, **464***, 471
 m -Nitraniline, 464*
 p -Nitraniline, 460, **464***, 471, 483, 489
 Nitraniline red, 495
 Nitric esters, 75, **112**
 Nitriles, **187**, 749, 835
 See also Cyanides
*iso*Nitriles, **189**
 See also *iso*Cyanides
 Nitriles, lithium salts, 730
 Nitrilium halides, 188
 Nitroacetanilides, 464
 Nitroacetic acid, 138
 o -Nitroacetophenone, 569
 Nitroaminophenol ethers, 469
 Nitrobenzaldehydes, 411, 570, 611
 Nitrobenzene, 418, **421***, 454, 612
 Nitrobenzene sulphate, 419*
 Nitrobenzene sulphonic acids, 415, 426
 Nitrobenzoic acids, 375, **533***, 535
 p -Nitrobenzoic acid, esters, 95 533
 Nitrobenzyl chloride, 900
 Nitrobromobenzoic acid, 375

- Nitrobutylglycerol, 141
 Nitrocellulose, 364, 486
 Nitrochlorobenzenes, 415
 Nitrocinnamic acids, **526***, 569, 784
 Nitrocinnamic amide, 764
 Nitro-compounds, 7, 127
 —, aliphatic, 111, 112, 128, **137**
 —, aromatic, **418**, 479, 592, 811
 —, —, reduction of, **451**, 471, 481, 496, 497
 Nitrocyclopentane, 643
 Nitroethane, 138*
 Nitroethylene, 141*
 Nitro-fatty acids, 138
 Nitroform, 141
 Nitrogen, 3
 —, detection of, 4
 —, divalent, 499
 —, micro determination of, 9
 —, quantitative estimation of, 6
 Nitrogen compounds, stereochemistry of, 134, 475, 484, 511, 524, 691
 Nitroglycerin, **310**
 Nitro-hydroxybenzoic acid, 375
 Nitrohydroxylamine, 166
 Nitrolic acids, 140, 238
 Nitro-lime, 236
 Nitromethane, 15, 132*, 841, 913
 Nitromethylanilines, 472
 Nitromethylcyclobutane, 643
 Nitromethylcyclohexanone, potassium salt, 106
 Nitron, 802*
 Nitronaphthalene, 405, 461
 Nitronic acids, 139, 422
 Nitropenta, 313
 Nitrophenols, 447*, 464, 468
 Nitrophenol ethers, 448
 Nitrophenyl-nitromethane, 422
 Nitrophenylpropionic acid, 569
 Nitrophthalic acid, 405
 Nitropropane, 138*
 Nitropyridine, 807*
 Nitrosamines, **132**, **455**, 480, 496
 Nitrosamine red, 495
 Nitrosates, 56
 Nitrosites, 56
*iso*Nitrosoacetone, 258
*iso*Nitrosobarbituric acid, 279
 Nitrosobenzene, 422
 Nitroso blue, 622
*iso*Nitroso camphor, 701
 Nitrosochlorides, 56
 Nitroso-compounds, aliphatic, 7, 136
 —, aromatic, **422**, 481
 Nitroso-dimethylaniline, 133, **455**, 461, 582, 616, 621
 Nitroso-diphenylhydroxylamine, 423
*iso*Nitrosoindoxyl, 568
*iso*Nitroso-isoxazolone-oxime, 239
*iso*Nitrosoketones, 769
 Nitroso methyl urethane, 294
 Nitroso-naphtholsulphoric acid, 449
 Nitrosophenol, **582***, 621, 629
 Nitroso-phenylhydroxylamines 480
 Nitrostilbene-carboxylic acid, 411
 Nitrothiophene, 765*
 Nitrotoluenes, 419, **421**, 534
 Nitrotoluene sulphonic acid, 494
 Nitrous acid, esters, 111, 138
 Nomenclature, 24
 See also Geneva nomenclature
 Nonadecane, 30*
 Nonadecylic acid, 193*
 Nonadienal, 172
 Nonane, 23, 30*
 Nonane-dicarboxylic acid, 198, 274*
 Nonoses, 347
 Nonyl alcohol, 85*, 108
 Nonylamine, 131*
 Nonylene, 52*
 Nonylic acid, 217
 See also Pelargonic acid
 Norbixin, 713
 Norcaradiene carboxylic ester, 387, 744
 Norcarane, 744*
l-Nor-ephedrine, 839
 Nor-*d*-pseudo-ephedrine, 839
 Nor-hydroxyhydrastinine, 884, 885
 Norhyoscyne, 858
 Norlaudanosine, 908
 Norleucine, 97, 287, 289*, 302
 Normal forms, 24
 Normuscol, 751
 Normuscione, 751
 Nornicotine, 844
 Norpinic acid, 651, 697
 Norscopolamine, 858
 Nortropine, 857
 Norvaline, 287, 302
 Nosophene, 610
 Novatophan, 815
 Novocaine, 244, **248**, 535
 Nucleic acids, 304, 308, 823, **829**, 832
 Nucleophilic atom, 64
 Nucleophilic substitution, 388
 Nucleoproteins, 30, 308, 829
 Nucleosides, 830, 832
 Nucleotides, 830, 832
 Numbering of heterocyclic ring systems, 757
 Nylon, 281
 Ocimenes, 62, 698
 Octacosanol, 108
 Octadecane, 30*
 Octadecylene-(1), 51*
 Octahydro-acridines, 631
 Octahydro-anthracene, 410
 Octamethylene bromide, 196
 Octamethylene diamine, 250
 α -Octamylose, 359
 Octanes, 23, 30*, **36**, 40, 52
n-Octane, 846
 Octane number, 36, 40
 Octenes, 36, 51*
 Octoses, 347
 Octyl acetate, 211*
 Octyl alcohols, 85*, 108
 Octyl amine, 131*
 Octyl butyrate, 211*
 Octyl cyanide, 188*
*iso*Octyl-dihydrocupreine, 851
 Octylenes, see Octenes
d-Octyl nitrate, 106
 Odours, classification, 933
 Oenanthal, 160*, 169
 Oenanthic acid, 169, 193*, 194*, 203, 217
 Oenanthic anhydride, 222*
 Oenanthone, 174*
 Oenanthyl chloride, 221*
 Oestradiol, 718*, 723
 Oestriol, 717*, 718
 Oestrone, 717, 718, 719, 723
 Oiazine, 756
 Oils, **213**
 Oleanolic acid, 727
 Olefins, see Ethylenes
 —, nomenclature of the, 49
 Oleic acid, 204, 205, 206, **208***, 214, 218
 —, series, 205
*iso*Gleic acid, 216
 Oleodistearin, 214
 Oleopalmitostearin, 214

- Oligosaccharides, 350
 Olivetol, 542
 Ommochromes, 787
 Onium compounds, 125
 Opianic acids, 879, 881, 884
 Opium alkaloids, 877, 879, 882, **888**
 Oppanol, 741
 Opsopyrrole, 772*
 Opsopyrrole-carboxylic acid, 782
 Optical activity, **98**, 915
 Optoquine, 874
 Orange I, II, and III, 488
 Orcein, 438
 Orcinol, **437***, 540, 542
 β -Orcinol, 542
 Organogenic elements, 3
 Orleans, 492
 Ornithine, 251, 287, 288, 289*, 291, 302, 906
 Ornithuric acid, 293, 521
 Orseille, 438
 Orsellinic acid, 540*
Ortho-, 382
 Orthocarbonic acid, 227
 Orthocarboxylic acid, 190
 Orthocarboxylic esters, **220**, 225
 Orthoformic esters, 159, 175, 183, 220
 Oryzenin, 307
 Osamine, 332
 Osazones, see Phenylsazones, etc.
 Oscine, 858
 Osmic acid, esters, 55
 Osmophoric group, 160
 Osones, 332, 343
 Osotetrazines, 800, 836
 Ovalbumin, 308
 Ovalene, 413
 Ovoglobulin, 307
 Oxalacetic acid, 277, **316***, 320, 917
 Oxalacetic ester, **316***, 490
 Oxalic acid, 1, 2, 109, 198, 199, 265, 274*, **275**, 614, 838
 —, salts and complexes, 276
 Oxaluric acid, 276
 Oxalyl chloride, 276*
 Oxalyl urea, see Parabanic acid
 Oxamic acid, 276
 Oxamide, 276
 Oxanilide, 515
 Oxanthranol, 591
 Oxazines, 438, 544, **621**
 Oxazoles, 298, 468, 756, **790**
 Oxazolines, 298, 790
 β -Oxidation, 197, 217
 w -Oxidation, 198
 Oximes, 56, 130, 249, 325, 504, 511
 See also Aldoximes, Dioximes, Ketoximes
 Oximes, stereochemistry of, 511, 691
 Oxindole, 784
 Oxindone-carboxylic ester, 644
 Oxonium compounds, 126
 Oxonium salts, 116, 561, 562, 621, 681, 805
 —, tertiary, 118
 Oxycellulose, 365
 Oxygen, 3
 —, detection of, 5
 —, heavy, 911
 —, quantitative determination of, 5
 —, tetravalent, 117
 Oxygen activator or carrier, 504, 585, 772
 Oxyhaemoglobin, 772, 773
 Ozokerite, see Mineral wax
 Ozonides, 55, 207, 387, 640
 Paeonidin, 564
 Paeonin, 564
 Paeonol, 517
 Palatine fast dyes, 492
 Palmital plasmalogenes, 219
 Palmitic acid, 33, 193*, 203, **204**, 214, 217, 218, 711, 716
 Palmitic aldehyde, **160***, 219
 Palmitic amide, 224*
 Palmitic anhydride, 222*
 Palmitone, 174*
 Palmitonitrile, 188*
 Palmityl chloride, 221*
 Panthesine, 248
 Pantothenic acid, 733, 737
 Papain, 307
 Papaverine, **876***, 877, 908
 Papite, 926
Para-, 382
 Parabanic acid, 276*, 796
 Parachor, 122
 Paracodin, 892
 Paracyanogen, 272
 Paraffins, **22**, 383
 —, nomenclature, 23
 —, occurrence and preparation, 26
 —, properties, 30
 Paraffin wax, 41, 217
 Paraformaldehyde, 166
 Parafuchsin, 165, 609, **611**, 614
 Parafuchsin-leuco-sulphonic acid, 165
 Paraldehyde, 168
 Paramagneti m, 400
 Pararosanine, see Parafuchsin
 Paraxanthine, 828
 Patent blue, 611
 Pauly's reaction, 306
 Pectins, 361
 Pegan, 899
 Peganine, 899
 Pelargone, 174*
 Pelargonic acid, 33, 193*, 203, 204
 Pelargonic aldehyde, 160*, 169
 Pelargonidin, 563, 564
 Pelargonidin methyl ethers, 564
 Pelargonin, 563
 Pelargonyl chloride, 221*
 Pelletierines, 862–864
 Pellotine, 874*
 Penaldinic acids, 792
 Penicillamine, 792, 793
 Penicillins, 304, 792
 Penicillinase, 793
 Penicilloic acids, 793
 Penilloaldehydes, 793
 Pentabenzoyl glucose, 324
 Pentacene, 413
 Pentacetyl glucose, 324, 327, 328
 Pentachlorethane, 252*
 Pentachloronaphthalene, 405
 Pentacontane, 30*
 Pentacosane, 30*
 Pentadecane, 30*
 Pentadecyl cyanide, 188*
 Pentadecylic acid, 193*
 Pentadeutero benzoic acid, 914*
 Pentaerythritol, 313
 Pentaerythritol tetranitrate, 313
 Pentahydroxy-benzene, 441
 Pentamannoside, 367
 Pentamethylbenzene, 394*
 Pentamethylene bromide, 241, 242*, 652
 Pentamethylene chloride, 242*
 Pentamethylene diamine, 251* 806
 Pentamethylene glycol, 247*
 Pentamethylene oxide, 244
 Pentamethylene tetrazole, see Cardiazole
 Pentanal- α , β - d_2 -diethylacetal, 912

- Pentane, 23, 30*, 35
 Pentanitraniline, 465*
 Pentaphenyl chromium hydroxide, 155
 Pentaphenylethane, 399, **401**
 Pentaryt, 313
 Pentatriacontane, 30*
 Pentene, 54
 Pentitols, 313
 Pentosans, 361, 362, 759
 Pentoses, 321, 331, **334**, **344**, 441, 731, 758, 759
 Pentoses, detection of, 330
 Pentrite, 313
 Pentyl, 313
 Pepsin, 286, **307**
 Peptidases, 307
 Peptones, 306, 307
 Peracetic acid, **223**, 390
 Peracids, aliphatic, 222
 Perbenzoic acid, 123, 504, **522***
 Perbunan, 741
 Perbutyric acid, 223*
 Percaine, 815
 Perchlorethane, 252*
 Perchlorethylene, 252*
 Perchloronaphthalene, 407
 Perfumes, minimal concentrations detectable by their smell, 933
 Perhydroanthracene, 410
 Perillaldehyde, 682
 Periodic acid oxidation, 246, 342, 690
Peri-position, 407
 Perkin's synthesis, 205, **525**, 538
 Pernigraniline, 585
 Peroxides, organic, 118
 Perseitol, 314*
 Pervitine, 463
 Perylene, 409*
 PetN, 313
 Petrol, 39, 41
 —, artificial production, 42
 Petroleum, see Mineral oil
 pH intervals, 940
 Phaeophorbides, 780
 Phaeoporphyrin-a₅, 779
 Phalloidine, 787
 Phaseolin, 307
 Phellandrenes, 668, 669*, 670
 Phenacetine, 470*
 Phenaceturic acid, **293**, 525
 Phenanthraquinone, 393, 459, **590***, 617
 Phenanthrene, 384, **411***, 762, 888
 Phenanthrene-9-carboxylic acid, 411
 Phenanthrenequinones, 590*
 Phenanthrophenazine, 616
 Phenates, 429, 430
 Phenazines, 458, 459, **615**
 Phenazineazonium salt, 586
 Phenazoxonium salts, 615
 Phenazthionium salts, 615, **623**
 Phencarboxonium salts, 615
 Phencarbthionium salts, 615
 Phenetidines, 469
 Phenetidine red, 495
 Phenetidineurea, 470*
 Phenetole, 432*, 478
 Phenocyanines, 623
 Phenol, 293, 373, 374, 385, 390, **431***, 478, 582, 609, 674, 913
 Phenols, 39, 383, 426, **427**, 473, 506, 554, 575
 —, dihydric, 429, **434**, 636
 —, polyhydric, 430, 441, 506, 510, 551, 661, 913
 Phenols, trihydric, 439
 "Phenol-betaine", 798
 Phenoldisulphonic acid, 434, **446**
 Phenol-glucuronic acid, 347
 Phenolic esters, 431
 Phenolic ethers, **430**, 483, 506, 510, 524
 Phenolphthalein, 609
 Phenolsulphonic acids, **444**, 547
 Phenoquinone, 579
 Phenosafranine, 619
 Phenoxazine salts, 615, 621
 γ -Phenoxy-propyl bromide, 865
 Phenthiazine salts, 615, **623**
 Phenyl isocyanate, 229, 470
 Phenyl cyanide, see Benzonitrile
 Phenyl ethyl ketone, 839
 Phenyl iodochloride, 415
 Phenyl methyl diketone, 840
 Phenyl radical, 373
 Phenylacetaldehyde, 526
 Phenylacetic acid, 193, 197, 293, 411, **524***
 —, esters, 387, 450, 525, 744
*iso*Phenylacetic ester, see Cycloheptatriene carboxylic acid
 Phenylacetoneitrile, 189
 See also Benzyl cyanide
 Phenylacetylene, 403
 Phenylacrosazone, 343
 Phenylalanine, 287, 288, 289*, 303, 306, 901
 Phenyl-aminomethyl-carbinol 816
 Phenyl-aminopropionic acid, 299
 Phenylarsine dichloride, 500
 Phenylarsonic acid, 477
 Phenyl-benzo-pyrones, see Flavones
 Phenylbenzylcarbinol, 503
 Phenylbutyric acid, 197
 Phenyl-(*p*-carboxymethoxy-phenyl)-butyl-phosphine-sulphide, 143
 Phenylcarbylamine, 513
 Phenyl-chloro-iodonium chloride, 415
 Phenylcinchoninic acid, 815
 Phenylisocrotonic acid, 406
 Phenyldiazonium xanthate, 426, 477
 Phenyldihydrothebaine, 894
 Phenyldimethylpyrazole, 260
 Phenyldimethylpyrazolone, see Antipyrine
 Phenylene blue, 584
 Phenylene radical, 458
o-Phenylenediamine, 428, **458***, 617
m-Phenylenediamine, **460***, 487, 493, 616, 617, 631
p-Phenylenediamine, **460***, 490, 493, 580, 583, 616, 617, 619, 624
 Phenylethyl isothiocyanate, 241
 Phenylethylalcohol, 450*
 β -Phenylethylamine, 462, 816, 840
 Phenylethylurethane, 470
 Phenylfulvene, 653
 Phenyl glucosides, 328
 Phenylglycine, 570
 Phenylglycine carboxylic acid 570, 784
 Phenylhydrazine, **480***, 497
 Phenylhydrazine sulphonic acid, 490
 Phenylhydrazones, **162**, **176**, 505, 511, 784
 —, of sugars, 325, 344
 Phenylhydroxylamine, **423***, 466
 Phenylmethylacetic acid, 525
 Phenylmethylcarbinol, 503
 Phenylmethylpyrazoles, 797
 Phenylmethylpyrazolone 270, 798

- Phenyl-naphthalene dicarboxylic ester, 527
- Phenyl-nitromethane, 139, **421***
- Phenyl-nitrosamine, 475
- Phenylosazones, 255, 800, 836
—, of sugars, 325, 332
- Phenyloxazoline-carboxylic ester, 790
- Phenylphenazonium salts, 617
- Phenylphosphine, 500
- Phenylphosphine dichloride, 500
- Phenylphosphinic acid, 500
- Phenylphosphonic acid, 500
- Phenylpiperidinium salts, 135
- Phenylpropionic acid, 403, **527***
- Phenylpropionic acid, 197
- Phenylpropyl alcohol, 450*
- Phenylpyrroles, 768, 771
- 2-Phenylquinoline-4-carboxylic acid, 793
- Phenylstibonic acid, 477
- Phenyl-thioglycol-*o*-carboxylic acid, 477, 574, 767
- Phenylurethan, 231, **470***, 523
- Phenylvaleric acid, 197
- Phenylxanthic ester, 426, **477**
- Phlobaphen, 567
- Phloionic acid, 281
- Phloracetophenone methyl ethers, 518, 559
- Phloretic acid, 537*
- Phloretin, 537
- Phloridzin, 537
- Phlorin, 537
- Phlorobenzophenone, 511, 518
- Phloroglucinaldehyde dimethyl ether, 565
- Phloroglucinol, 428, 430, **440***, 559, 563, 660, 759, 762, 913
- Phloroglucinol trimethyl ether 440
- Phloroglucitol, 661, **674***
- Phlorrhicin, 537
- Phloxin, 636
- Phoenicin, 581
- Phorone, 176, 178
- Phosgene, 182, **228***
- Phosphagen, 295
- Phosphatases, 351
- Phosphatides, 218
- Phosphazines, 143
- "Phosphine", 633
- Phosphines, 141
- Phosphine oxides, **142**
- Phosphine sulphides, 142
- Phosphinimines, 143
- Phosphobenzene, 500*
- Phospho-glyceric acids, 91, 360
- Phosphonic acids, **142**, 500, 831
- Phosphonium compounds, 142
- Phosphoproteins, 304, 308
- Phosphopyruvic acid, 93, 91, 360
- Phosphoric esters, 74, **114**
- Phosphorus, quantitative estimation of, 8
- Phosphorus organic compounds of, 141, 500
- Phthalic acids, 405, 407, 409, **529***, 530*, 817
- Phthalic anhydride, **529***, 594, 609, 634, 636, 813
- Phthalides, 530
- Phthalimide, **529**, 534
- Phthalocyanines, 788
- Phthalonitrile, 788
- Phthalyl chlorides, 530*
- Phthiocol, 588*, 737
- Phyllo-aetioporphylin, 778
- Phylloerythrin, 779
- Phylloporphyrin, 779
- Phyllopyrrole, 772*
- Phyllopyrrole carboxylic acid, 782
- Phylloquinone, 736
- Physalien, 711
- Physicon, 599
- Physodic acid, 542
- Physostigmine, 903
- Phytic acid, 675
- Phytin, 676
- Phytol, **111***, 736, 778
- Phytosterols, 713, 715
- Phytoxanthins, 710
- Piazine, 756, 817
- Piazselenole, 459
- Piazthiole, 459
- Picein, 517
- Picene, 412*
- Picolines, 809*, 810, 846, 864
- Picolinic acid, 811*, 846
- Picramic acid, 449
- Picrates, 449
- Picramide, 464, 465*, 473, 483
- Picric acid, 420, 429, 446, 448, **449***, 838, 901
- Picrolonic acid, 838
- Pilocarpines, **901***, 904
- Pilopic acid, 901
- Pilosine, 902
- Pimelic acid, 198, 274*, 275, **281**, 385, 536, 640, 854
- Pimelic acid, ester, 639
- Pimelic acids, alkyl substituted 683, 688, 744
- Pimpinellins, 763
- Pinacols, 62, 174, 243, 640
- Pinacoline, 175
- Pinacoline rearrangement, 175, 645
- Pinacones, see Pinacols
- Pinane, 693, 696, 698
- Pinastric acid, 528
- Pinenes, 669, 696*, 698, 702
- Pinene hydrochloride, **698**, 702
- Pinic acid, 697
- Pinitol, 676
- Pinocarveol, 698
- Pinocarvone, 698
- Pinole, 697
- Pinole hydrate, 697
- Pinonic acid, 697
- Pinosylvins, 444
- Pipecolines, 811
- Pipecolinic acid, 848
- Piperazine, 250, **821***
- Piperazine derivatives, 822
- Piperic acids, 543*, 851
- Piperidine, 241, 250, 806, 810* 851
- Piperidine dicarboxylic acids, 811
- Piperidinium salts, 134
- Piperine, 851*
- Piperitol, 679, 680*
- "Piperitone", 684
- Piperolidine, 848
- Piperonal, **509***, 543
- Piperonylic acid, 540*
- Pitch, 41, 42, 383
- Plasmal, 219
- Plasmalogene, 219
- Plasmochine, 871
- Plastics, 79, 168, 364, 403, 432
- Platinum, organic compounds of, 155
- Poisonous compounds in industry, 934
- Poisonous gases and vapours, 936
- Poisonous substances, limits of tolerance of human beings, 937
- Poisonous substances used in warfare, 935
- Polar bond, 63
- Polarization, 64
- Polyamines, 428
- Polygalacturonic acids, 361
- Polyglucosamines, 349
- Polyglyoxal, 257
- Polymerism, 24

- Polymerizations, 57, 59, 61, 79, 163, 403, 651, 788
 Polymethine dyes, 807
 Polymethylenes, 39, **637**
 Polymethylene compounds, stereochemistry, 647, 650, 651, 748
 Polymethylene dibromides, **242**, 639
 Polynucleotides, see Nucleic acids
 Poly-oxymethylenes, 166
 Polypeptides, **296**, 306, 307, 901
 Polyporic acid, 580
 Polysaccharides, 356
 Polysiloxanes, 147
 Polystyrene, 403,
 Polyterpenes, 704, 713
 Polythenes, 57
 Ponceau 2 R, 488
 Populin, 451
 Poroidines, 857
 Porphyrazines, 789
 Porphyrins, 38, **774**, 778
 Potassium carbonyl, 442
 Potassium ethyl succinate, 281
 Potassium ferrocyanide, 184
 Potassium imidazole, 794
 Potassium indole, 785
 Potassium phenyl-*isopropyl*, 156
 Potassium phthalimide, 529
 See also Gabriel's synthesis
 Potassium pyrrole, 769, 781
 Pregnanediols, 720, 723
 Pregnanedione, 720
 Pregnanes, 720, 724
 Pregnanolones, 720, 721, 723
 Pregnenolone, 723
 Prehnitene, 394*
 Prehnitene sulphonic acid, 394
 Prehnitic acid, 531*
 Primary carbon atom, 24
 Primuline, 626, 630
 Primuline yellow, 629
 Primverose, 355, 592
 Progesterones, 720, 723
 Projection formulæ, 107
 Proline, 287, 288, 289*, 302, 303, 304, 307, 308, 768, 782*, 842, 901, 918
 Prontalbin, 466
 Prontosil (rubrum), 487
 Propaesin, 535
 Propane, 23, 30*, **35**
 Propargyl alcohol, 111*
 Propargyl aldehyde, 172
 Propargyl halides, 78
 Propene, see Propylene
 Propiolactone, 263
 Propiolic acid, 210*
 Propionaldehyde, 160*, 848
 Propionamide, 224*
 Propione, 174*
 Propionic acid, 194*, **201***, 646, 898, 915, 916
 Propionic anhydride, 222*
 Propionyl chloride, 221*
 Propional, 279
 Propyl alcohols, 57, 84, 85*, 94, **95**
 Propyl bromide, 74*
 Propyl chloride, 74*
 Propyl chlorocarbonate, 229*
 Propyl cyanide, 188*
 Propyl iodides, 35, 74*, **77**, 79, 645
 Propyl mercaptan, 119*
 Propyl nitrite, 138*
 Propylacetylene, 67
 Propylamine, 131*
 Propylbenzene, 392*
n-Propyl-boric acid, 151*
 Propylene, 42, 45, 52*, 309, 391, 645
 Propylene bromide, 242*
 Propylene chloride, 57, **242***
 Propylene glycol, **246***, 256
 Propylene iodide, 79
 Propylguaiaicol, 365
*iso*Propylidene-adenosine, 831
 Propylpyridine, 846, 863
 Prosthetic group, 91
 Prostigmine, 904
 Protachysterol, 735
 Protagon, 219
 Protamines, 308
 Proteids, 304
 Proteins, 7, 91, **304**, 776, 829, 901, 918
 —, hydrolysis of, 286, 298, 821
 Proteinogenic amines, 291, 837, 840
 Prothrombin, 736
 Protocatechuic acid, 365, **539***, 559, 564
 Protocetraric acid, 542
 Protocotoin, 518*
 Protopine, 896, 897*
 Protoporphyrin, 773, 775
 Prunicyanin, 563
 Prussian blue, 4, **186**
 Prussic acid, see Hydrocyanic acid
 Pschorr synthesis, 411
 Pseudo-acids, 139, 422
 Pseudo-asymmetric carbon atom, 313, 856
 Pseudoatropine, 856
 Pseudo-bases, 607
 Pseudo-nitrols, 141
 Pseudo-nitrosites, 56
 Pseudopelletierine, 746, 856, 863*, 908
 Pseudoracemic mixed crystals, 102
 Pseudo-salts, 191
 Pseudo-uric acid, 279, 824
 Psicose, 338
 Psychotrine, 903
 Psyllastearic acid, 203
 Pteridine, 833
 Pterins, 739, 833
 Pterostilbene, 444
 Pteroylglutamic acid, 739
 Pteroyl polyglutamates, 739
 Ptomaines, 251
 Pulegenic acid, 643
*iso*Pulegol, 684
 Pulegones, 643, 667, 684*
 Pulvinic acid, 528
 Purine, 823
 Purine compounds, **823**, 830
 Purple of the Ancients, 573
 Purpureagluco-sides, 725
 Purpuric acid, 825
 Purpurin, 594, 597
 Purpurogallin, 439
 Putrescine, **251***, 291
 Py-, 844
 Pyoctanin, 613
 Pyocyanine, 617
 Pyramidone, 799
 Pyrans, 562, 756, 804
 Pyranoses, 324
 Pyranthrone, 602
 Pyrazine, 817, **821***
 Pyrazine derivatives, 820
 Pyrazoles, 756, **796***
 Pyrazole blue, 798
 Pyrazole tricarboxylic ester, 796
 Pyrazolidines, 797
 Pyrazolines, 294, 647, 797
 Pyrazolones, 316, 490, 797
 Pyrazolone dyes, 799
 Pyrene, 384, **412***
 Pyrethrin, 655
 Pyrethrolone, 655
 Pyridazine, 756, **817**
 Pyridine, 383, 431, 756, **806***
 Pyridine derivatives, 39, 384, 771, 791, 806
 Pyridine homologues, **f**

- Pyridine carboxylic acids, 808, 811*, 844, 846
 Pyridine dicarboxylic acids, 811*
 Pyridine sulphonc acid, 807
 Pyridine tricarboxylic acids, 811*, 815
 Pyridinium salts, 808
 Pyridiums, 808
 Pyridones, 808
 Pyridoxal, 733
 Pyridoxine, 732
 Pyridylacetic ester, 865
 Pyridylpyrrole, 844
 Pyrimidine, 270, 817, 819*
 Pyrimidine derivatives, 818, 824, 830
 Pyrocatechol, 428, 429, **434***, 462, 539, 576, 594
 —, metallic derivatives, 435
 Pyrocolls, 781
 Pyrogallol, 429, **439***, 621, 636
 Pyrogallol carboxylic acid, 544*
 Pyrogallol dimethyl ether, 439, 581
 Pyrogene indigo, 628
 Pyroglutamic acid, 783
 Pyroligneous acid, **87**, 581
 Pyromeconic acid, 806
 Pyromellitic anhydride, 532
 Pyromucic acid, 758, 759, 760*
 Pyrones, 550*, 554
 Pyronine, 633
 Pyroxonium compounds, 562
 Pyrro-ætioporphyrin, 778
 Pyrrole, 280, 755, 758, 768, **769***
 Pyrrole aldehyde, 770
 Pyrrole homologues, 771
 Pyrrole magnesium salts, 770, 843
 Pyrrole ketones, 770
 Pyrrole carboxylic acids, 768, 770, 781
 Pyrrolidine, 250, 769, 781*, 843
 Pyrrolidine carboxylic acids, 782
 Pyrrolidone carboxylic acid, 783*
 Pyrroline, 781*
 Pyrromethanes, 776
 Pyrroporphyrin, 779
 Pyrrolacetic ester, 770
 Pyruvic acid, 91, **266***, 286, 320, 360, 917
 —, esters, 106, 281
 —, sodium compounds, 562
 Qualitative analysis, 3
 Quantitative analysis, 5
 Quaternary ammonium bases, 133, 453
 Quaternary ammonium salts, 125, 134, 453
 Quaternary carbon atom, 24
 Quebrachitol, 676
 Quercetagenin, 558
 Quercetin, **557***, 566
 Quercitol, 662, **675***
 Quercitrin, 557
 Quinaldine, 813*, 815
 Quinazoline, 899
 Quinethyline, 874
 Quinhydrone, 438, **579**, 617
 Quinic acid, 543, 579, 662, **689**, 838, 873
 Quinicine, 870
 Quinidine, 104, 548, 865, **874***
 Quinine, 104, 548, 838, 865, **869***, 871, 874
 Quininic acid, 814, 869, 870, 871
 Quinone, 869, 871
 Quinitols, 674*
 Quinizarin, 594, 596, 600
 Quinodimethane, 605
 Quinol, see Hydroquinone
 Quinolimine, 479
 Quinoline, 384, 756, 785, **811**, 812*–815, 867, 901
 —, alkaloids, 865
 —, derivatives, 871
 —, homologues, 39, 812, 813*, *iso*Quinoline, 384, 811, **816**, 817*
 —, alkaloids, 874
 —, homologues, 39
 Quinoline carboxylic acids, 814
 Quinoline dicarboxylic acid, 631
 Quinoline yellow, 813
 Quinolinic acid, 811*, 812
 Quinolinium compounds, 815, 817
 Quinolones, 815
 Quinols, 577
 Quinomethane, 605
 Quinone, see *p*-Benzoquinone
 Quinones, 429, **576**, 661
 Quinone dyes, closed ring, 615
 Quinoneimines, 580, **582**
 Quinone oximes, 582
 Quinotannic acid, 547
 Quinotoxine, 870, 871
 Quinovin, 345
 Quinovose, 345
 Quinoxalines, 459
 Quinpropyline, 874
 Quinuclidine derivatives, 866, 867
 Quitenine, 869
 Racemates, 102
 —, partial, 104
 Racemic acid, see Tartaric acids
 R-acid, 447, **488**
 Radical, 18
 Radical theory, 2, 18
 Radical type substitution, 388
 Radioactive isotopes, 911
 Raffinose, 355*
 Raman spectra, 381
 Rancidity of fats, 178, 217
 Rapanone, 581
 Rapid dyes, 496
 Rapidogen, 496
 Ratanhine, 288
 Rayon, **367**, 485
 Refraction, atomic, 52, 941
 —, molecular, 52
 —, —, exaltation or increment, 53, 66, 246, 380, 750
 Reimer-Tiemann synthesis, 506
 Resacetophenone, 517*
 Reserve cellulose, see Lichenin
 Resins, artificial, 72, 79, 148, 168, 232, 432
 Resites, 432
 Resoles, 432
 Resolution of optically inactive substances, **103**, 122, 134, 149, 277
 Resonance, 379
 Resorcinol, 428, 430, **437***, 562, 621, 635, 762, 913
 Resorcinol dimethyl ether, 389
 Resorcylic acids, **540***, 559
 Restricted rotation, 396, 512, 771
 Resveratrol, 444
 Retene, **412***, 707
 Retronecanone, 846
 Retronecine, 846
 Rhamnazetin, 558
 Rhamnetins, 558
 Rhamnitols, 314
 Rhamnose, **345***, 563, 902
 Rhapontin, 444
 Rhein, 599*
 Rhodamines, 634
 Rhodamine B, 634
 Rhodanilic acid, 782
 Rhodeose, see Fucose

- Rhodinol, 110
 Rhodizonic acid, 676
 Rhodoporphyrin, 779
 Ribodesose, 830
 Riboflavin, 730
 —, phosphate, 732
 Ribose, **334, 345**, 730, 830, 831
 Ribose phosphates, 830, 831, 832
 Ribo-trihydroxyglutaric acid, 335
 Ricin, 307
 Ricinic acid, 852
 Ricinine, 851
 Ricinoleic acid, **209***
 Ring contraction, 642
 Ring expansion, 643
 Ring fissure, energy of, 246*
 Rivanol, 633
 Robison ester, see Glucose-phosphate
 Rochelle salt, 319
 Rodinal, 468
 Rongalite C, 168, 572
 Rosamine, 634
 Rosaniline, see Fuchsin
 Rose Bengal, 636
 Rosinduline, 618
 Rosolic acid, 609
 Rotation, optical, 98
 Rotenone, 764
 Rubber, 672, 739
 —, artificial, 189, 741
 Rubeanic acid, 273
 Ruberythric acid, 592
 Rubrene, 412
 Rufigallic acid, 597
 Rutaecarpine, 899*

 S acid, see Schöllkopf
 Sabinene, 693*
 Sabinaketone, 693
 Sabinenic acid, 694
 Sabinol, 695
 Sabromin, 255
 Saccharase, 352
 Saccharic acid, 330, 337, 339*, 346, 348, 760
 Saccharic acids, 325, 676
 Saccharin, 533*
 Saccharose, see Sucrose
 Safflower, 492, 520
 Safranines, 585, 617, **618**
 Safroles, 436*, 509
 St. Denis red, 494
 Saiodin, 255
 Salazinic acid, 542
 Salicin, 451*, 507
 Salicylaldehyde, **507***, 538
 Salicylic acid, 373, 375, 491, **535***, 555, 561
 —, allyl ester, 77
 Salicyl-tropeine, 857
 Saligenin, 451*
 Salmin, 308
 Salol, 537*
 Salsoline, 875
 Salt colours, 493
 Salvorsan, 502
 Sambunigrin, 548
 Sandmeyer's reaction, 414, **478**
 Santalene, 707
 Santonin, 707*, 863
 Saponification, 212, **215**, 917
 Saponins, 715, 727
 Sapotalene, 727
 Sarcolactic acid, 262*, 303
 Sarcosine, 295
 Sarsasapogenin, 727, 902
 Sarsasapogenoic acid, 903
 Schäffer's (β)-acid, **447**, 589
 Schiff's base, 129
 Schiff's reagent, 165
 Schöllkopf acid, 447, 467
 Schotten-Baumann acylations, 431, 522
 Schweinfurter Green, 201
 Scillaridin, 725
 Scleroproteins, 308
 Scopine, 858
 Scopalamine, 858*, 907
 Scopoletin, 552
 Scopolin (glucoside), 552
 Scopoline (alkaloid), 858
 Scopolinic acid, 811
 Scutellarein, 555
 Scutellarin, 555
 Scyllitol, 664, 676*, 677
 Sebacic acid, 198, 208, 274*, **281**
 Secondary carbon atom, 24
 Sedanolic acid, 691
 Sedanolid, 691*
 Sedoheptitol, 314
 Sedoheptose or Sedoheptulose, 347
 Selachyl alcohol, 310
 Selenophen, 766*
 Selinene, 706
 Seliwanow's reaction, 760
 Semiacetals, 162
 Semicarbazide, 162, 235, 834
 Semicarbazones, 163, 176, 511
 Semidine bases, 498
 Semidine rearrangement, 498
 Semihydrobenzoin transformation, 175
 Semipinacoline transformation, 175
 Semipolar double bond, 122, **127**, 416
 Semiquinone, **583**, 617
 Septanose, 324
 Serines, 286, 289*, 302, 303, 308
 Serinealdehyde, 793
 Serine phosphate, 288
 Serum albumin, 305, 307
 Serum globulin, 305
 Sesquiterpenes, 704
 Sex hormones, 717
 Shikimic acid, 691
 Shikonin, 589
 Shogaol, 518
 Silanediols, 147
 Silanes, **145**
 Silicic esters, 114*
 Silicols, 147
 Silicon alkyl chlorides, 147
 Silicon compounds, aliphatic, **145**
 Silicones, 147
 Silicone resins, 148
 Silicononane, 146
 Silicononyl alcohol, 146*
 Silicononyl chloride, 146
 Silk, 308, 485
 Silk, artificial, 367
 Silk (natural and artificial), production, 937
 Siloxanes, 147
 Silvan, 758*
 Silver fulminate, 238
 Silver methyl, 155
 Silver phenyl, 155
 Sinalbin, 241
 Sitosterol, 715
 Skatole, 292, 783, 786*
 Skatoleacetic acid, 786
 Skatole carboxylic acid, 786
 Skraup's synthesis, 596, 811
 Soaps, 113, 204, 215, **216**
 Sobrerol, 697
 Sodium-alkyls, 29, **156**, 191
 Sodium ammonium tartrate, 103*, **317**
 Sodium aryls, 503
 Sodiumbenzyl, 503
 Sodium *n*-butyl, 156
 Sodium cellulose, 366
 Sodium cyanamide, 176, **235**
 Sodium cyanide, 4, **185**, 186
 Sodium dodecyl, 156
 Sodium ethyl, 156
 Sodium ethylate, 86
 Sodium ferricyanide, 186
 Sodium ferrocyanide, 4, **185**
 Sodium formate, 198

- Sodium indenyl, 404
 Sodium indole, 785
 Sodium methyl, 156
 Sodium nitroprusside, 186
 Sodium octyl, 156
 Sodium propyl, 156
 Sodium triphenylmethyl, 503
 Solanidanol, 902
 Solanidenone, 902
 Solanidine, **902***
 Solanine, **902***
 Solar oil, 41
 Solid green O, 582
 Sorbitol, 114, 314*, 339, 734
 Sorbose, 338, 344, **347***, 734
 Sovprene, 741
 Sozoiodol, 446
 Sparteine, 864, 865*
 Specific rotation, 98
 Spermidine, 251
 Spermine, 251
 Sphærophorol, 542
 Sphingomyelin, 219, 249
 Sphingosine, 249
 Spiranes, 691
 Spirit blue, 614
 Spirit eosin, 636
 Spirocid, 502
 Spirographis-hæmin, 776
 Spiroheptane dicarboxylic acid, 691*
 Squalene, 58
 Stachydrine, 303, 842*, 905
 Stachyose, 356*
 Stannones, 149
 Stannonic acids, 149
 Staple rayon, 368
 Starch, 93, 354, **357**
 Stearic acid, 33, 193*, 203, **204**, 214, 217, 218, 716
 Stearic aldehyde, **160***, 219
 Stearic amide, 224*
 Stearic anhydride, 222*
 Stearin, 215, **217**
 Stearolic acid, 210
 Stearone, 174*
 Stearonitrile, 188*
 Stearyl chloride, 221*
 Stereochemistry, carbon compounds, 21, 98, 300, 333, 408, 663, 690, 748
 See also other elements and
 Cis trans isomerism
 Stereo-formula, 24
 Steric hindrance, 396, 511, 527
 Steroid alkaloids, 902
 Sterols, 713
 —, configuration, 715, 722
 —, cubine oxides, aryl, 503
 Stibines, alkyl, 145
 Stibino-compounds, 503
 Stibonic acids, 477, **503**
 Stibonium salts and bases, 145
 Stigmasterol, 715, 721
 Stilbenes, 284, **403***
 Stilbene derivatives, 444, 720
 Stilboestrol, 720
 Stovaine, 248
 Stovarsol, 502
 Strain theory, **245**, 742, 748, 750
 Strainless ring-forms, 408, 742, 749, 750
 Strecker's synthesis, 285
 Streptidine, 677
 Streptobiosamine, 677
 Streptomycin, 677
 Strophanthidin, 725
 Strophanthin, 725
 K-Strophanthoside, 726
 Structural formulæ, 14, 24
 Structural theory, 21
 Strychnine, 104, **904**
 Styphnic acid, 437, **449***, 838
 Styracine, 451
 Styrene, 79, 384, **402***, 526, 741
 Styrene, 451
 Suberic acid, 198, 274*, 275, **281**, 742, 751, 863
 Suberone, see Cycloheptanone
 Suberyl alcohol, see Cycloheptanol
 Suberylamine, 743
 Substantive dyes, 486, 492
 Substituents, directing effects, 416
 Substitution, 19, 32
 Substitution of benzenes, mechanism, 387
 Substitution isomerism of aliphatic compounds, 77
 —, of benzenes, 381
 Succindialdehyde, 258, 771, 855, 860
 Succinic acid, 1, 93, 274*, 278, **279**, 320, 708, 848, 914*, 917
 —, ester, 662, 669
 —, salts, 765
 Succinic acids, alkyl substituted, 685, 700, 709, 710, 711
 Succinic anhydride, **280**, 634, 914*
 Succinic anhydride-d₄, 914*
 Succinimide, 280, 768
 Succino-succinic ester, 662, 669
 Succinyl chloride, 280
 Sucrose, 351, **352***
 Sugar anhydrides, 359
 Sugar esters, 545, 712
 Sugars, 2, 441
 —, α and β forms, 339
 —, configuration, 326, 330, **333**, 339
 Sugars, degradation, 331
 —, epimeric, 329, 332
 —, furanose (or γ) forms, 324
 —, interconversion, 329, 332
 —, inversion of, 329
 —, properties, 325, 344
 —, open chain forms, 324
 —, world production, 931, 932
 —, pyranose (or normal) forms, 324
 —, septanose forms, 324
 —, synthesis, 332, 342
 —, tautomerism, 757
 Sulphanic acids, 452, 471
 Sulphamidobenzoic acid, 533*
 Sulphanilamide, 466
 Sulphanilic acid, **465**, 488
 Sulphapyridine, 808
 Sulphathiazole, 792
 Sulphine oxides, see Sulphoxides
 Sulphinic acids, aliphatic, 122, 124
 —, aromatic, **425**, 503
 Sulphinic esters, 122
 Sulphobenzoic acid, 533
 Sulphonal, 123, **177**
 Sulphonamides, aryl, 425
 Sulphon-cyanine black B, 489
 Sulphones, **123**, 124, 126
 Sulphonic acids, aliphatic, **113**, **123**
 —, aromatic, **425**, 428
 Sulphonium compounds, 121, 122, 126
 Sulphonyl chlorides, 124, 425
 Sulphoraphene, 123
 Sulphoxides, 122, **123**, 126
 Sulphur, quantitative estimation of, 8
 —, stereochemistry, 122
 Sulphur compounds, aliphatic, 119
 Sulphur dyes, 574, **626**
 Sulphuric acid, chlorides, 124
 —, acid esters, 50, 54, 82, **112**, 115
 —, neutral esters, 113, 128, 430
 Sulphurous acid, esters, **113**, 123

- Sumach, 547
 Supramine reds, 489
 Suprasterols, 735
 Surinamine, 288, 863
 Sweetness of organic substances, 932
 Sylvestrene, 672*
 Symmetrical (*s*), 382
 Syntholine, 233
 • Synthesis, total, 27
 Syringic acid, **545***, 564
 Syringic aldehyde, 366
 Syringidin, 564
- Tachysterol, 735
 Tagatose, 338
 Talitol, 339*
 Talo-mucic acid, 338, 339*, 676
 Talose, **337**, 338, 339*, 341
 α -Tanacetogen dicarboxylic acid, 648, 693
 Tanacetone, see β -Thujone
 Tannalbin, 547
 Tannic acid, 486
 Tannigen, 547
 Tannins, 322, **545**, 565, 566, 567, 838
 —, artificial, 168, 432, 547
 Tannin reds, 567
 Tannoform, 547
 Tartar emetic, 318
 Tartaric acids, 1, 102, 104, 255, 266, 283, 311, **317***, 333, 838
 —, salts, 280, **318**
 Tartrazine, 490, 799
 Tartronic acid, 315*
 Taurine, 247
 Taurocholic acid, 247, 293, 716
 Tautomerism, **109**, 137, 185, 226, 235, 448, 582, 591, 615, 660, 783, 797, 801, 814, 819, 880, 913
 See also Keto-enol
- Tea, 547
 Teacatechin, 567*
 Tectorigenin, 560
 Terebic acid, 648, 679, 680
 Terephthalaldehyde, 748
 Terephthalic acid, 531, 748, 895
 Teresantalic acid, 707
 Terpenes, 39, 198, 579, 637, **693**, 740
 Terpenylic acid, 680
 Terpins, 669, 670, 679, **681***, 682, 694
- Terpin hydrate, 679, **681**, 698
 Terpinenes, 666, 667, **668**
 Terpinenols, 679, 680*
 Terpeneols, 104, 110, 669, 670, 671, **679**, 680*, 698
 Terpinolene, 668, 670*
 Terpinolene tetrabromide, 670*
 Terthienyl, 766
 Tertiary carbon atom, 24
 Testicular hormones, 721
 Testosterone, 722*, 723
 Tetracetyl-bromoglucose, 328
 See also Acetobromoglucose
 Tetracetyl-chloroglucose, 328
 Tetraalkylammonium salts, 124
 Tetraanisylhydrazine, 499*
 Tetrabromocyclohexadienone 432
 Tetrabromophenolphthalein ethyl ester, 487
 Tetracene, 413
 Tetrachlorethylene, 252*
 Tetrachloro dideutero ethane, 914*
 Tetrachloroethane, 70, 252*, 914*
 Tetrachlorophthalic acid, 405
 Tetracontane, 37
 Tetracosane, 30*
 Tetradecane, 30*
 Tetradeuteromalonic acid, 914*
 Tetra-(*p*-dimethylamino-) tetraphenylhydrazine, 499
 Tetraethylammonium, 131
 Tetraethyl orthosilicate, 114*
 Tetraethyl silane, 146*
 Tetrahedral symmetry of carbon atom, 99
 Tetrahydroanthracene, 410
 Tetrahydrobutylidene-phthalide, 530
 Tetrahydronaphthalene, 407*
 Tetrahydronaphthol, 104
 Tetrahydro- β -naphthylamine, 861
 Tetrahydronicotinic acid, 851
 Tetrahydroquinolines, 813*
 Tetrahydroisoquinoline, 816, 817*
 Tetrahydrosalicylic acid, 536
 Tetrahydroxybenzenes, 441*, 677
 Tetrahydroxydiaminobenzene, 442
 Tetrahydroxyquinone, 676, 677
- Tetralin, 407*
 Tetramannoside, 367
 Tetramethyl orthosilicate, 114*
 Tetramethylacetone, 441
 Tetramethylammonium hydroxide, 133
 —, salts, 133
 Tetramethyl-diarsine, 144
 Tetramethylene bromide, 241, 242*
 Tetramethylene chloride, 242*
 Tetramethylene diamine, 251, 771, 818
 Tetramethylene glycol, 247*
 Tetramethylene oxide, 244
 Tetramethyl-ethylene diamine 889
 Tetramethylglucose, 351, 359
 Tetramethylmethane, 146*
 Tetramethyl-methylglucoside, 327
 Tetramethylpiperidone, 857
 Tetramethylsilane, 146*
 Tetramethyluric acid, 827
 α -Tetramylose (or α dextrin), 359
 Tetranitrobenzenes, 421
 Tetranitrodiphenic acid, 396
 Tetranitromethane, 141*
 Tetranitrotoluene, 421
 Tetraoxymethylene, 166
 Tetraphenylallyl, 401
 Tetraphenylchromium salts, 155
 Tetraphenyl-dicyclohexylethane, 401
 Tetraphenyl-dimethylmethane, 401
 Tetraphenylethane, 399, 401
 Tetraphenylethylene, 404
 Tetraphenylhydrazine, 499*
 Tetraphenylmethane, 399*
 Tetraphenylquinodimethane, 605, 606*
 Tetraphenylrubrene, 412
 Tetrasaccharides, 356
 Tetrasalicylide chloroform, 183
 Tetrazines, 756, **836**
 Tetrazole, 756, 803*
 Tetrazones, 136
 • Tetritols, 313
 Tetrollic acid, 210
 Tetronal, 178
 Tetronic acid, 760
 Tetroses, 321, **334**, **344**
 Textiles, world production, 937

- hebaine, 248, **893***
 hebainone, 893
 hebaol, 893
 hebenine, 893
 Heine, 828
 Theobromine, 827*
 Theocine, 827
 Theolactin, 828
 Theophylline, 827*
 Therapinic acid, 215
 min, 729
 nin pyrophosphate, 92,
 J
 Thiazine, 623*
 Thiazine dyes, 623, 626
 Thiazoles, 627, 756, 791
 Thiazolidines, 792
 Thiazolines, 792
 Thiazolinium salts, 729, 792
 Thiazthionium chloride, 576
 Thio-acids, 195
 Thioalcohols, see Mercaptans
 Thioamides, 791
 Thioaminoacetals, 793
 Thiocoumarone, 755
 Thiocyanic acid, **273***, 273
 —, esters, 132, **240**, 479
 —, salts, 230, **239**, 273, 795
*iso*Thiocyanic acid, 239
 —, esters, 132, 229, 239, **240**
 Thiocyanogen, 273*
 Thiodiglycolic acid, 623
 Thiodiphenylamine, **456**, 623*
 625, 627
 Thio-ethers, **121**
 Thioformamides, 791, 792
 Thioglycolic acid, 477
 Thioglycols, 247
 Thioindigo (Thioindigo red
 B), 574, 767
 Thioindigo derivatives, 576
 Thioindigo Scarlet R, 575
 Thioindogenides, 767
 Thioindoxyl, 574, 575
 Thioisatin, 571
 Thionaphthene, 766*
 Thionaphthene-indolindigo,
 575
 Thionylamines, 471
 Thiophan derivatives, 738
 Thiophen, 71, 280, 385, 755,
 758, **764**, 768
 Thiophenols, **426***, 627
 Thiophen sulphonic acid, 765
 Thiophthen, 39, 766*
 Thiopyran, 756, 804
 Thiosalicylic acid, 477, 574
 Thiosemicarbazide, 162
 Thiotolens, 393, 766
 Thioureas, 234*
 Thiourea, alkyl derivatives,
 234
 —, aryl derivatives, 454, 470
 Thioxanthylum salt, 615
 Thioxens, 766
 Threitol, 312
 Threonine, 287, 288, 289*, 302
 Threose, 312, **334**, **344**
 Thujane, 693
 Thujenes, 693
 Thujones, 693, **694***, 695
 Thujylalcohol, 695
 Thymidine, 830
 Thymine, 819, **820***, 830
 Thymol, **433***, 679, 683
 Thymo-nucleic acid, 830, 831,
 832
 Thyroxine, **539**, 724
 Tiglic acid, 208*
 Tiglic aldehyde, 170*
 Tigogenin, 727
 Tin, organic compounds of,
 148, 149
 Tin tetraethyl, 148*
 Tin tetramethyl, 148*
 T.N.T., 419
 Tocopherols, 736
 Tolane, 403*
 Tolidine, 492
 Toluene, 52, 383, **392***, 504,
 521
 Toluene musk, 394, 421
 Toluene sulphonic acids, 424,
 533
 Toluene sulphonic acid methyl
 ester, 88, 425
 Toluenesulphonyl chloride,
 128, 431
 Toluic acids, 524, 898
 Toluidine, 433, **457***, 613, 619
m-Toluidine, 489
p-Toluidine, 600, 612, 613,
 629
 Tolusafranine, 619
 Toluylene blue, **585**, 616
 Toluylene red, 616
 Tolylenediamines, 460*, 619,
 632
 Tonophosphan, 500
 Toxins, 251
 Toxisterol, 735
 Tracers, 911
 Transamination, 918
 Transesterification, 87, 214
 Trehaloses, 350, **354***
 Triacetoneamine, 179, 857, 861
 Triacetonane, 37
 Triacetonol, 108
 Triaminobenzene, 428, 440
 Triaminohydroxypyrimidine,
 739, 833
 Triaminopyrimidine, 826
 Triarylmethyls, 105, **401**
 Triazines, 237, 756, **834**
 Triazine tricarboxylic acid,
 835
 Triazoles, 756, 800, 801*, 802*,
 836
 Tribiphenyl-methyl, 401
 Tribromohydrin, 214
 See also Tribromopropane
 Tribromophenol, 445*, 913
 Tribromophenyl hypobromite
 432
 Tribromopropane, 214, 308,
 319
 Tributyrin, 215
 Tricaprin, 198
 Tricarballylic acid, **319***, 691,
 766
 Trichloroacetic acid, **254**
 Trichloroacetone, 177
 Trichloroaniline, 463
 Trichlorobenzenes, 417*
 Trichloroethyl alcohol, 253
 Trichloroethylene, 78, 252*
 Trichloromethyl perchlorate,
 228*
 Trichlorophenol, 445
 Trichloro-phenomalic acid,
 391
 Trichlorophenylmethyl sul-
 phate, 608
 Trichloropurine, 826, 828
 Tricin, 557
 Tricosane, 30*
 Tridecane, 30*
 Tridecylamine, 131*
 Tridecylic acid, 193*
 Triethyl silicon chloride, 146
 Triethylsilanol, 147
 Triethylphenylmethane, 146*
 Triethylphenylsilane, 146*
 Triethylstibine 145*
 Trigonelline, 849
 Trihydroxyanthraquinones,
 597
 Trihydroxycyclohexanone,
 689
 Triiodoacetone, 177
 Triiodophenol, 445*
 Triketohydrindene, (hydrate)
 (ninhydrin) 306, **516**
 Trimellitic acid, 531*, 895
 Trimesic acid, 531*
 Trimethoxy-biphenyl dicar-
 boxylic acid, 894

- Trimethylacetic acid, 202*
 Trimethylamine, 76, **133**, 184
 Trimethylammonium-9-fluorenylide, 134
 Trimethylammonium methide 134
 Trimethylisoamylsilane, 146*
 Trimethylarsine, 144
 Trimethylbismuthine, 145*
 Trimethylbutane, 36*
 Trimethylbutylsilane, 146*
 Trimethylcarbinol, 46
 "Trimethyl-colchicinic acid", 895
 Trimethylene, see Cyclopropane
 Trimethylene bromide, **242***, 639, 645, 649
 Trimethylene chloride, 242*
 Trimethylene diamine, 250, 251*
 Trimethylene glycol, 247*
 Trimethylene oxide, 244
 Trimethylethylmethane, 146*
 Trimethylethylsilane, 146*
 Trimethylfructose, 361
 Trimethylglucoses, 351, 359, 361
 Trimethylinulin, 361
 Trimethyllyxose, 329
 Trimethylmannose, 367
 1:2:7-Trimethylnaphthalene, 727
 Trimethylpentane, see *iso*-Octane
 Trimethylphenylmethane, 146*
 Trimethylphenylsilane, 146*
 Trimethylpropylsilane, 146*
 Trimethylstarch, 359
 Trimethylstibine, 145*
 Trimethylsuccinic acid, 699
 Trimethyl-trimethylene-triamine, 163
 Trimethylxylose, 329
 Trinitrate, 141
 Trinitroamines, 421
 Trinitrobenzene, 419, 420, 421*
 Trinitrobenzene-hexamethylbenzene, 420
 Trinitrostilbene, 420
 Trinitro-(ter, butyl)-xylene, 421
 Trinitrochlorobenzene, 427
 Trinitrodiphenic acid, 396
 Trinitromethane, 141
 Trinitrophenol, see Picric acid
 Trinitroresorcinol, 437
 Trinitrotoluene, 419, 421*
 Triolein, 214*
 Trional, 178
 Triose phosphate, 90, 350
 Trioses, 321
 Trioxymethylene, 166
 Tripalmitin, 213*
 Triphenylamine, 456*
 Triphenylaminoguanidine, 802
 Triphenylarsine, 501*
 Triphenylcarbinol derivatives, 606
 Triphenyliodomethane, 400
 Triphenylisoxazole, 513
 Triphenylmethanes, **399**, 505, 612
 Triphenylmethane dyes, 606
 Triphenylmethyl, 131, **400**
 Triphenylmethylchloride, 399, 400, **401**
 Triphenylmethyl peroxide, 400
 Triquinoyl, 442, 656
 Trisaccharides, 355
 Tristearin, 214*
 Triterpenes, 59
 Triticin, 361
 Triundecylin, 198
 Tröger base, 135
 Tropacocaine, 862*, 907
 Tropane, 856
 Tropeines, 857
 Tropic acid, 549*, 853, 856, 857
 Tropidine, 743, 855, 859
 Tropigenine, 854
 Tropilidene, see Cycloheptatriene
 Tropines 743, 853-859 (856*)
 Tropinic acid, 783, 854, 859, 860
 Tropinone, 854, 856, 859, 860, 907
 Tropinone carboxylic acid, 859
 Trotyl, see T.N.T.
 Truxillic acids, 651, 861
 Truxillines, 862*
 Truxinic acids, 651
 Trypaflavine, 632
 Tryparsamide, 501
 Trypsin, 286, **307**
 Tryptamine, 841, 898
 Tryptophan, 287, 288, 289*, 306, 728, 768, 783, 786, 841
 —, 5-ethoxy, 904
 Tschugaeff, see Zerewitinoff
 Tubaic acid, 764
 Tuberculo-stearic acid, 2*
 Turanose, 353*
 Turicine, 842*, 905
 Turkey red oil, 595
 Turmeric, 492, 521
 Turpentine-oil, 696
 Tutocaine, 248
 Twitchell process, 216
 Types, theory of, 19, 20
 Tyramine, 291, 463, 840*
 Tyrian Purple, 1, **573**
 Tyrosine, 287, 288, 289*, 303, 306, 539, 840
 Uliron, 466
 Umbelliferone, 551*
 Undecane, 30*, 33
 Undecane dicarboxylic acid, 274*
 Undecyl alcohol, 85*
 Undecyl aldehyde, 169
 Undecyl amine, 131*
 Undecyl bromide, 196
 Undecylenic acid, 208*
 Undecylic acid, 193*, 208
 Unsaturated acids, 197, 207, 217, 281, 525, 796
 —, esters, 818
 Unsaturated aliphatic alcohols, 108
 Unsaturated aliphatic aldehydes, 169
 —, hydrocarbons, 43
 —, ketones, 178
 Uracil, 819, **820***, 830
 Uramil, 279, 825
 Urates, 825
 Urea, 1, **231***, 233, 818, 825, 917
 Urea chloride, 230
 Urea formaldehyde resins, 2*
 Urea, mercury derivative, 2*
 Urea nitrate, 232
 Urea oxalate, 232
 Ureas, 136, 233, 470
 Urease, 232
 Ureides, 233, 820
 Ureido acids, 305
 Ureidobarbituric acid, Pseudo-uric acid
 Urethane, see Ethyl carbamate
 Urethanes, 130, 229, 232
 Uric acid, **823**, 828, 915
 —, salts, 825
 Uricase, 824
 Uridine, 830, 832
 Uridylic acid, 830, 832
 Urobilin, 777

- 53, 347
 174
 22
 78
 21
 f 62,
 16.
 2, 194*, 202*,
 dride, 222*
 de, 221*
 7, 288, 289*, 308
 540*, 564
 derivatives, 878
 435, 436, 507*,
 hyl ketone, 366
 584, 601, 626
 540*, 838, 858,
 hyde, 881
 5*, 877
 tropine, 858
 556*
 672
 ismarck brown
 45*
 1, 382
 5
 49
 S, 490
 cess', 200
 69
 108
 79
 79
 79, 108
 175
- Vinylite, 79
 Vinylquinclidone, 867, 868,
 870
 Vinyl radical, 79
 Vinylrhodoporphyrin, 778
 Violanin, 563
 Violanthrones, 603
 Violaxanthin, 711
 Violuric acid, 279
 Viruses, 829
 Viscose, 365
 Viscose rayon, 368
 Vistanex, 741
 Vitacamphor, 703
 Vital dye, 625
 Vital force, 2
 Vitamins, 727
 Vitamin A, 709, 728*
 Vitamin B₁, 729, 792
 Vitamin B₂, 730
 Vitamin B₆, 732
 Vitamin B (other), 733
 Vitamin C, 733
 Vitamin D, 734
 Vitamin D₂, 735
 Vitamin D₃, 735
 Vitamin D₄, 735
 Vitamin E, 736
 Vitamin K₁, 588, 736
 Vitamin K₂, 736
 Vitellin, 308
 Volemitol, 314*
 Vulcanization, 740
 Vulpinic acid, 528, 580
 Vuzine, 874
 Walden inversion, 300
 Water blue, 614
 Water type, 20
 Waxes, 212
 Weerman's reaction, 263
 Wood, 365
 Wood gas, 34
 Wood spirit, 88
 Wool, 485
 Wurster's red, 583
 Wurtz synthesis, 28, 391
 Xanthates, 51, 230, 426
 Xanthene, 561
 Xanthic acids, 230
 Xanthine, 826, 827, 830
 Xanthogenates, see Xanthates
 Xanthone, 554, 556, 561
 Xanthophyll, 709, 710, 778
 Xanthophyll mono-epoxide,
 711
 Xanthoproteic reaction, 306
 Xanthopterins, 833
 Xanthotoxin, 763
 Xanthydrol, 561
 Xanthylum salts, 615, 633
 Xeroform, 445
 Xylan, 345, 365
 Xylenes, 383, 392*, 393, 713
 Xylene musk, 421*
 Xylene yellow 3G., 799
 Xylenols, 384, 429, 433*
 Xylidines, 457*
 Xylitol, 313, 336
 Xyloketose, 344
 Xylonic acid, 344
 Xyloquinone, 578
 Xylose, 334, 343, 344, 345*,
 357, 592
 Xylo-trihydroxyglutaric acid,
 334, 336
 Yangonine, 806
 Yeast-adenylic acid, 831, 832
 Yeast glucan, 361
 Yeast-nucleic acid, 831, 832
 Yellow oxidation ferment, 730,
 731
 Yobyrine, 898
 Yohimbine, 898
 Yohimbone, 899
 Zeaxanthin, 710
 Zein, 307
 Zeisel estimation of ether
 groups, 431
 Zerewitinoff and Tschugaeff,
 estimation of active hydro-
 gen, 154
 Zinc alkyl salts, 154
 Zinc alkyls, 141, 144, 145, 148,
 149, 150, 154
 Zinc diamyl, 154*
 Zinc dibutyl, 154*
 Zinc diethyl, 75, 154*
 Zinc dimethyl, 154*, 650
 Zinc dipropyl, 154*
 Zingerone, 518*
 Zingiberene, 705
 Zoosterols, 713
 Zwitterion, 296, 802
 Zymase, 90
 Zymophosphate, see Harden-
 Young ester



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